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Transition Metal-Catalyzed Reductive C-C Bond Forming Hydrogenation/Transfer Hydrogenation and Applications in the Total Synthesis of (+)-Roxaticin

Committee:

Michael J. Krische, Supervisor

Philip D. Magnus

Alan H. Cowley

Sean M. Kerwin

Dionicio R. Siegel

Transition Metal-Catalyzed Reductive C-C Bond Forming Hydrogenation/Transfer Hydrogenation and Applications in the Total Synthesis of (+)-Roxaticin

by

Soo Bong Han, B.S.; M.S.

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Transition Metal-Catalyzed Reductive C-C Bond Forming Hydrogenation/Transfer Hydrogenation and applications in the Total Synthesis of (+)-Roxaticin

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By simply hydrogenating enones in the presence of aldehydes at ambient temperature and pressure, aldol adducts are generated under neutral conditions in the absence of any stoichiometric byproducts. Using cationic rhodium complexes modified by tri(2-furyl)phosphine, highly *syn*-diastereoselective reductive aldol additions of vinyl ketones are achieved. Finally, using novel monodentate TADDOL-like phosphonite ligands, the first highly diastereo- and enantioselective reductive aldol couplings of vinyl ketones were devised. These studies, along with other works from our laboratory, demonstrate that organometallics arising transiently in the course of catalytic hydrogenation offer byproduct-free alternatives to preformed organometallic reagents employed in classical carbonyl addition processes. Existing methods for enantioselective

carbonyl allylation, crotylation and tert-prenylation require stoichiometric generation of pre-metallated nucleophiles, and often employ stoichiometric chiral modifiers. Under the conditions of transfer hydrogenation employing an ortho-cyclometallated iridium C,O-benzoate catalyst, enantioselective carbonyl allylations, crotylations and tert-prenylations are achieved in the absence of stoichiometric metallic reagents or stoichiometric chiral modifiers. Moreover, under transfer hydrogenation conditions, primary alcohols function dually as hydrogen donors and aldehyde precursors, enabling enantioselective carbonyl addition directly from the alcohol oxidation level.

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1.1 INTRODUCTION

The polyene macrolide antibiotics consist of more than 200 members.[1] Some of these natural products such as nystatin, amphotericin B and pimaricin, have been used as medicine for a long time. For example, amphotericin B is used in the treatment of fungal infections; it forms ion channels in the cell to exhibit antifungal activity.[2] Many of the oxo polyene macrolide antibiotics are produced from antinomyces soil bacteria that

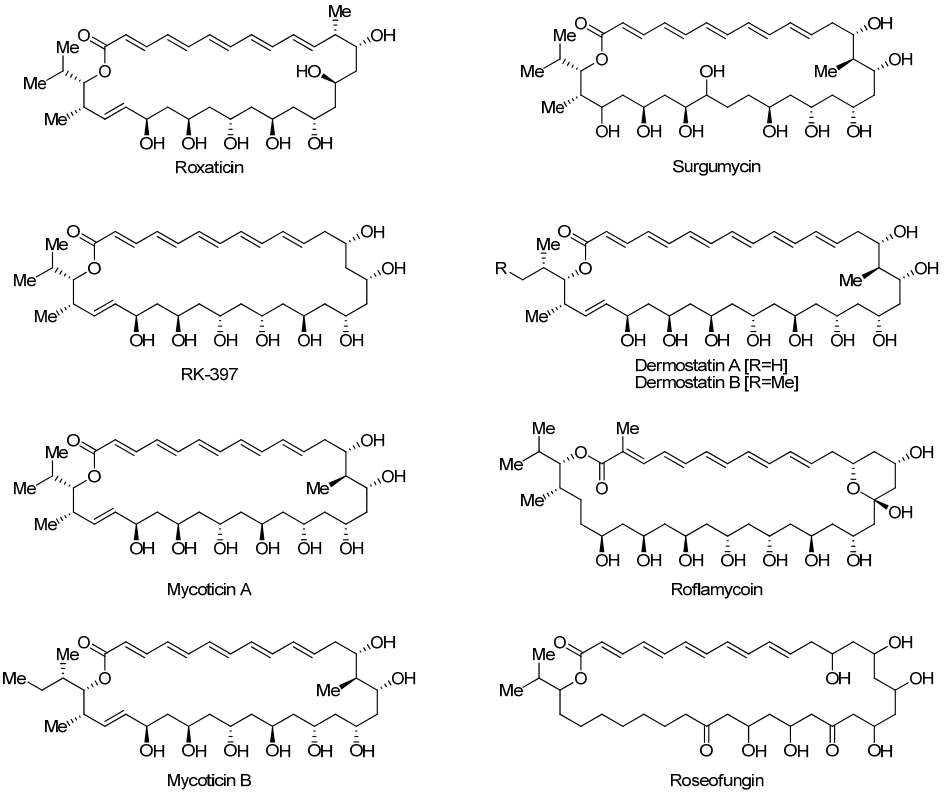


Figure 1.1 Representative examples of oxo polyene macrolides.

belongs to the genera *Strepotomyces*. Some of the oxo polyene macrolides are shown in Figure 1.1.

Among the oxo polyene macrolides, mycoticin was isolated and its structure was first determined.[3] Since then, many natural products of this family were isolated and their structures were revealed. Even though the structures of the members in this family are very challenging to make, many organic chemists have been attracted to their unique structures and efficacy as a medicine.[4] Amphotericin B was first synthesized among the class by Nicolaou in 1988.[5] The total synthesis of mycoticin A,[6] roxaticin,[7] filipin III,[8] roflamycoin,[9] RK-397[10] and dermostatin[11] then followed. Roxticin is the smallest member in the family, and was isolated in 1992.[12] Like the other members within its class, it also shows antifungal activity. The structure was determined by X-ray analysis of the heptaacetate derivative (Figure 1.2).[12] Similar to the family, it consists of alternating polyene chain and both *syn-, anti*-1,3-diol units; this interesting structure has been synthesized by Rychnovsky[7a], Mory[7b-d] and Evans groups.[7e] This review focuses on the total synthesis of roxaticin and methodologies employed for this construction.

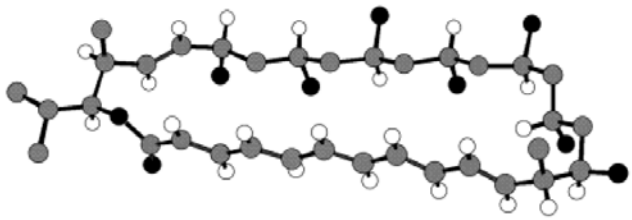
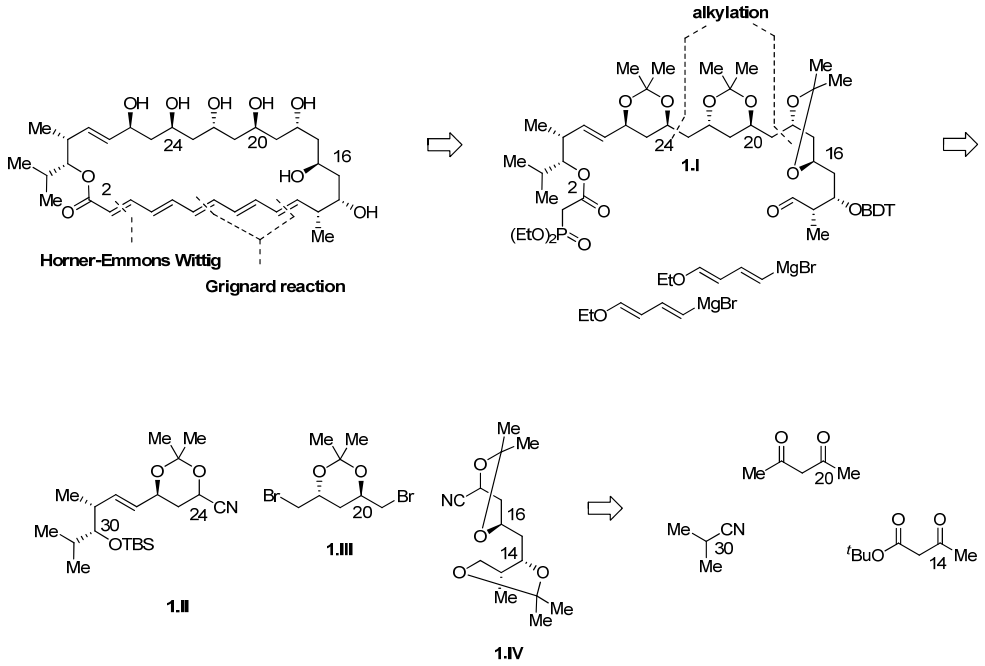


Figure 1.2 Roxaticin heptaacetate X-ray structure (acetates omitted for clarity).

1.2 SYNTHESIS OF (-)-ROXATICIN BY RYCHONOVSKY GROUP.

1.2.1 Synthetic plan

(-)-Roxaticin was first synthesized Rynchnovsky's group in 1994.[7a] The synthesis mainly used alkylation and reductive decyanation of cyanohydrin acetonides.[13] Due to the instability of the polyene fragment, it was introduced at the late stage of the synthesis. As shown in Scheme 1.1, the Horner-Emmons Witting reaction was exploited for macrocyclic ring formation. The polyene piece was synthesized through two sequential Grignard additions, leading to fragment **1.I**. C_{23}-C_{24} and C_{19}-C_{18} was connected by

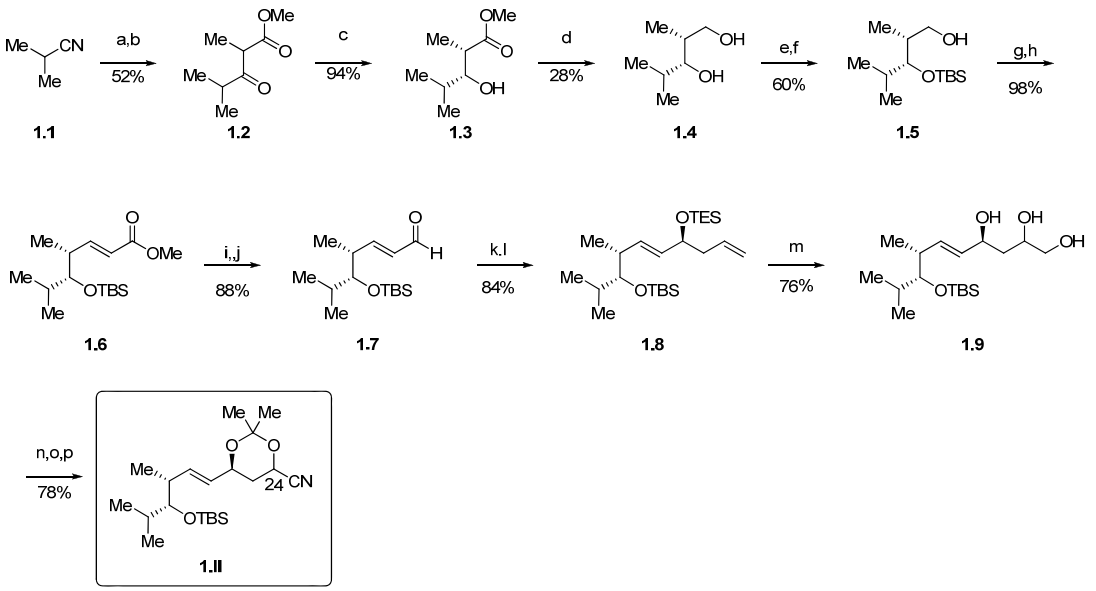


Scheme 1.1 Rychnovsky's retrosynthetic analysis of (-)-roxaticin.

alkylation reaction, resulting in three fragments **1.II**, **1.III** and **1.IV**. Fragment **1.II** was generated from isobutyronitrile *via* Blaise reaction, enantioselective reduction and Wittig coupling reaction. The dibromide **1.III** was synthesized from pentanedione.[14] The cyanohydrins acetonide **1.IV** was obtained from *tert*-butyl acetoacetate using Noyori's reduction[15] and Frater-Seebach alkylation.[16]

1.2.2 Synthesis of cyanohydrin aectonide fragment 1.II

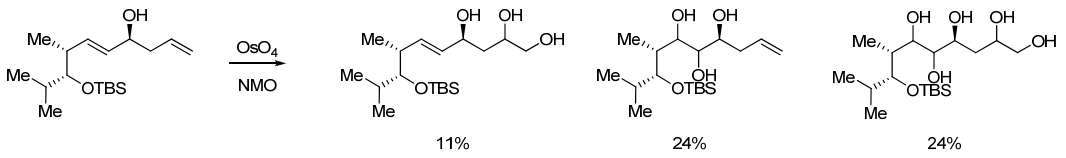
Rynchnovsky's group used Kishi's modified Blaise reaction[17] to construct 2,4-dimethyl-3-oxopentanonate **1.2**, which was proved to be very effective. [((*R*)-BINAP)$RuCl_2$]$_2$•Et_3N[18] was used for the enantioselective reduction of **1.2** (Scheme 1.2). Interestingly, 7:1 mixture of *syn*:*anti* products **1.3** were produced at 80 ^oC rather than previously reported 1:1 mixture of the products.[15] Because the reduction is slower than the epimerization of **1.2**, the reduction became more selective. The alcohol **1.3** was obtained in 94% yield and the enantioselectivity of the *syn* isomer was proved to 58% ee after Mosher's ester analysis.[19] Reduction of the ester and recrystallization afforded diol **1.4**, which was obtained in >98% ee. Even though the selectivity of asymmetric hydrogenation was moderate, this route was more practical than the route previously reported by Helqust[20] due to the facile recrystallization. Protection of both alcohols and selective deprotection produced monoprotected TBS ether **1.5**. The optically pure unsaturated ester **1.6** was obtained through Swern oxidation and Wittig reaction in 98% yield. DIBAL-H reduction of **1.6** and sequential Leys's catalytic oxidation[21] generated the corresponding aldehyde **1.7** in high yield. Brown's $Ipc_2BCH_2CH{=}CH_2$ reagent was



Key: (a) Zn, methyl 2-bromopropionate, THF; (b) H_3O^+; (c) (R-BINAP)$RuCl_2$, H_2, MeOH; (d) LAH,(80%), recrystallization (35%); (e) TBSOTf; (f) Dowex H^+, MeOH; (g) Swern; (h) $Ph_3P{=}CHCO_2CH_3$, CH_3CN, reflux; (i) DIBAL-H; (j) TPAP, NMO; (k) $Ipc_2BCH_2CH{=}CH_2$, NaOH, H_2O_2; (l) TESOTf, 2,6-lutidine; (m) OsO_4, NMO, HOAc, THF, H_2O; (n) $NaIO_4$; (o) K_2CO_3, $(CH_3)_2C(OH)CN$; (p) 2,2-DMP, CSA;

Scheme 1.2 Synthesis of cyanohydrin aectonide fragment **1.II**.

successfully applied for allylation of aldehyde **1.7** to set the last stereogenic center of **1.II**. Having the alcohol protected with TES group, dihydroxylation with OsO_4 was conducted to produce triol **1.9**. Direct oxidation from unprotected alcohol gave only 11% yield of product with other competitive oxidation side products (Scheme 1.3). Presumably bulky TES protecting group prevented the oxidation of the internal olefin.

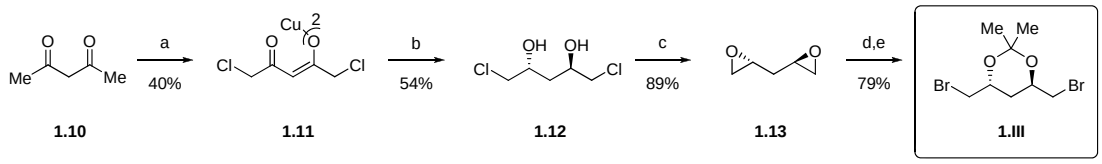


Scheme 1.3 Direct oxidation reaction.

Oxidative cleavage with $NaIO_4$, followed by cyanide exchange and acetonide protection produced fragment **1.II** in 78% yield from **1.9**.

1.2.3 Synthesis of dibromide fragment 1.III

The copper(II) complex **1.11** was isolated when 2,4-pentanedione **1.10** was treated with $AlCl_3$, $ClCH_2C(O)Cl$ and $Cu(OAc)_2$ (Scheme 1.4).[22] This crystalline complex **1.11** was asymmetrically hydrogenated using Noyori's catalyst[23] to produce diol **1.12** which was then treated with KOH to give diepoxide **1.13** in 89% yield. Dibromide **1.III** was prepared from diepoxide **1.13** in two step sequences. First the epoxide was opened with Li_2NiBr_4,[24] and the resulting diol was protected with acetonide.



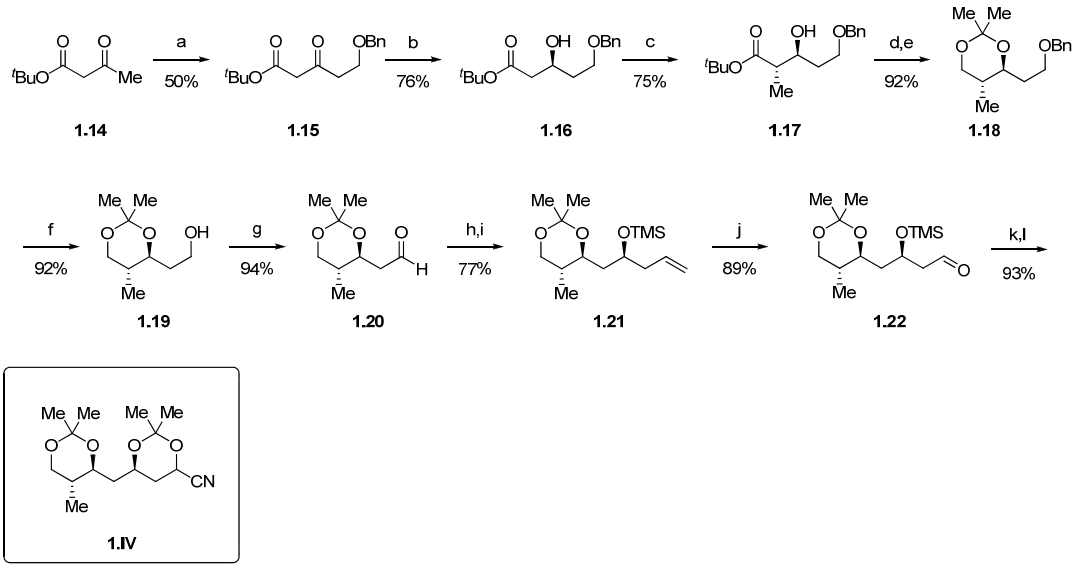
Key: (a) $AlCl_3$, $ClCH_2C(O)Cl$, 60 ^oC, $Cu(OAc)_2$; (b) H_3O^+, $[((S)\text{-BINAP})RuCl_2]_2Et_3N$, H_2 1200 psi, 120 ^oC, MeOH, recrystallize; (c) KOH, Et_2O; (d) Li_2NiBr_4, 25 ^oC, THF; (e) 2,2-DMP, CSA, Acetone

Scheme 1.4 Synthesis of dibromide fragment **1.III**.

1.2.4 Synthesis of cyanohydrins acetonide fragment 1.IV

β-keto ester **1.15** was synthesized by the alkylation reaction with NaH, *n*-BuLi and chlromethyl benzyl ether in 50% yield (Scheme 1.5). The ester **1.15** was then subjected to asymmetric hydrogenation with $[((R)\text{-BINAP})RuCl_2]_2 \bullet Et_3N$[18] prepared *in situ*. This reaction was improved when acidified with HCl at 45 ^oC.[25] The selectivity of

the reaction was 96% ee. The ester **1.16** was alkylated according to Frater-Seebach protocol,[16] which gave a 10:1 mixture of *anti* and *syn* isomers in 75% yield. Reduction of **1.17** and acetonide protection produced protected ether **1.18**. The benzyl group of **1.18** was cleaved using Pearlman's catalytic hydrogenation condition. The resulting alcohol **1.19** was oxidized and then subjected to Brown's allylation reaction, resulting in a single homoallylic alcohol product, which was isolated as TMS ether **1.21** after protection. Oxidation with OsO_4, cyanation with TMSCN and KCN/18-crown-6, followed by acetonide protection produced fragment **IV**.

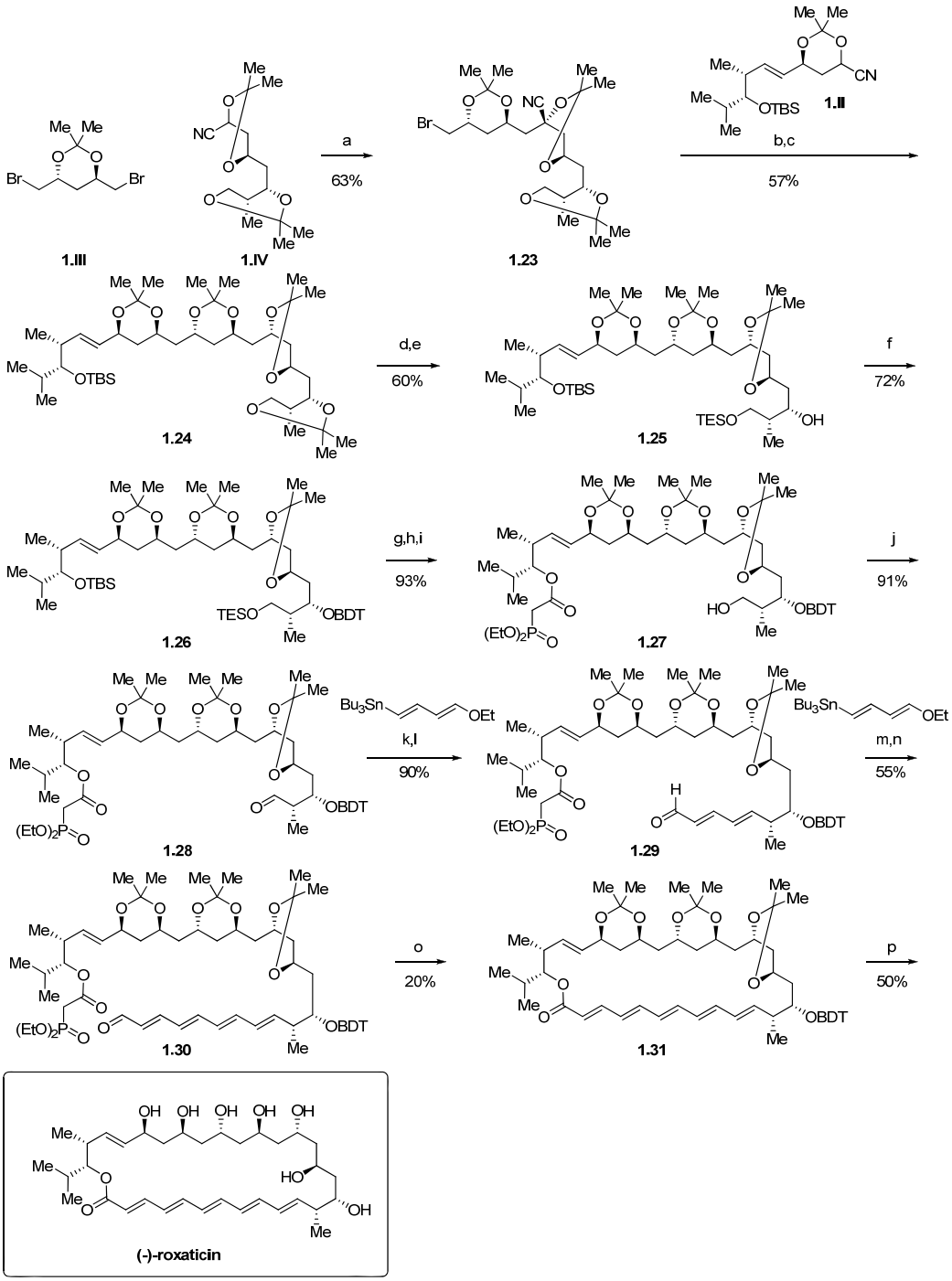


Key: (a) NaH, *n*-BuLi, chloromethyl benzyl ether; (b) H_3O^+, $[(S)\text{-BINAP})RuCl_2]_2Et_3N$, H_2 1620 psi, 45 °C, MeOH; (c) LHMDS, MeI; (d) $LiAlH_4$; (e) CSA, 2,2-DMP; (f) H_2, $Pd(OH)_2/C$; (g) Swern; (h) $Ipc_2BCH_2CH{=}CH_2$, NaOH, H_2O_2; (i) BSA, CH_3CN; (j) OsO_4, NMO, $NaIO_4$; (k) TMSCN; (l) 2,2-DMP, CSA

Scheme 1.5 Synthesis of cyanohydrin aectonide fragment 1.IV.

1.2.5 Endgame of (-)-roxaticin

The three fragments **1.II**, **1.III** and **1.IV** were combined by alkylation and



(a) $LiNEt_2$, THF; (b) $LiNEt_2$; (c) LiDBB, THF, MeOH; (d) TESOTf, *i*-Pr_2NEt; (e) OsO_4, *t*-BuOH, $CDCl_3$, pyridine; (f) 1,3-benzodithiolyl tetrafluoroborate, pyridine; (g) TBAF, THF; (h) $(EtO)_2P(O)CH_2CO_2H$, BOP, DMAP; (i) MeOH, NH_3; (j) Dess-Martin; (k) *n*-BuLi, $MgBr_2$, THF, -78 °C; (l) MsCl, Et_3N; (m) *n*-BuLi, $MgBr_2$, THF, -78 °C; (n) MsCl, Et_3N; (o) LiCl, DBU; (p) Dowex H^+, MeOH

Scheme 1.6 Endgame of (-)-roxaticin.

reductive decyanation protocols (Scheme 1.6). Dibromide **1.III** was alkylated with cyanohydrin acetonide **1.IV**. In this reaction, excess of the dibromide was used to avoid overalkylation. Similar reaction condition was used for the second alkylation of **1.23**, but **1.II** was used in 2-fold excess. Reductive elimination of the cyano group was performed with 10 equiv. of lithium di-*tert*-butylbiphenylide (LiDBB). Under these reaction conditions, the three fragments were successfully combined to afford tetraacetonide **1.24**. TES enol ether from **1.24** was obtained when the tetraacetonide **1.24** was treated with TESOTf and *i*-Pr_2NEt in DCM at 110 ^oC. The resulting enol ether was directly hydrolyzed with OsO_4 to give alcohol **1.25**. After protection of alcohol **1.25** with 1,3-benzodithiolyl tetrafluoroborate, deprotection of silyl groups and introduction of phosphonoacetate gave alcohol **1.27**. Dess-Martin oxidation produced the corresponding aldehyde **1.28**, which was then subjected to the modified Wollenberg polyene synthesis reaction.[26] The Grignard reagent generated from the corresponding tributyl tin was added to aldehyde **1.28** and the elimination was conducted with MsCl and Et_3N. The same sequence of the reaction was repeated to generate tetraenal **1.30**. For the cyclization reaction, Roush-Masamune cyclization protocol was used,[27] which gave cyclized product **1.31** in moderate yield. Grobal deprotection with Dowex H^+ gave (-)-roxaticin.

1.2.6 Summary

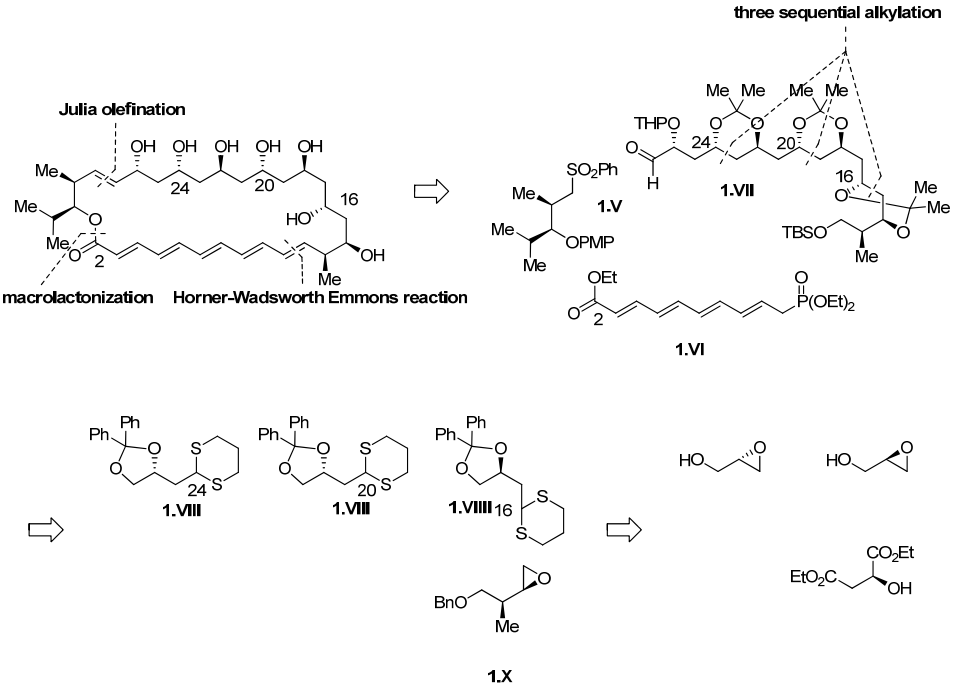
The unnatural (-)-roxaticin was first synthesized by Rychnovsk group. The synthesis was completed in 31 steps from isobutyronitrile (longest linear sequence), with a total number of 51 steps. Most of the stereogenic centers were constructed using Noyori

asymmetric hydrogenation, Rychnovsk's reductive decyanation, and Brown's enantioselective allylation reaction. Tthe first highly convergent synthesis of polyene macrolide antibiotics was achieved.

1.3 SYNTHESIS OF (+)-ROXATICIN BY MORY GROUP.

1.3.1 Synthetic plan

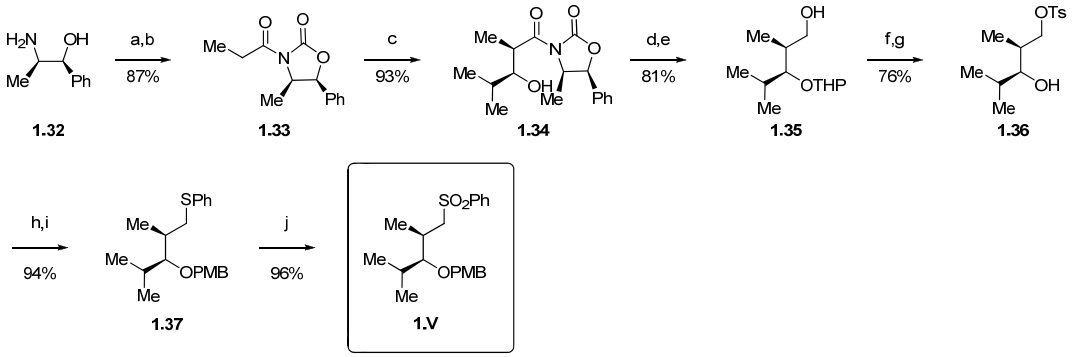
Mory's group synthesized the (+)-roxaticin in 1994.[7b,c,d] Their synthetic plan was shown in Scheme 1.7. The macrocyclic ring was formed using the Yamaguchi method.[28] Due to the light sensitive nature of the oxo pentaene moiety was introduced at the last stage using Horner-Wadsworth-Emmons protocol.[29] Internal olefin was generated *via* Julia olefination reaction.[30] These reactions led to fragments **1.V**, **1.VI** and **1.VII**. Fragment **1.VII** was formed from fragments **1.VIII**, **1.VIIII** and **1.X** through three sequential alkylation reactions. These three fragments were generated from (*S*), (*R*)-glycidols and (*S*)-diethyl malate.



Scheme 1.7 Mory's retrosynthetic analysis of (+)-roxaticin.

1.3.2 Synthesis of sulfone fragment 1.V

The sulfone fragment **1.V** was synthesized from **1.32** using Evan's auxiliary (Scheme 1.8).[31] Isobutryaldehyde was successfully coupled with **1.33** to give the aldol product **1.34** in 93% yield. Aldol compound **1.34** was protected with THP, and the auxiliary was cleaved with $LiAlH_4$ to produce primary alcohol **1.35**. Direct cleavage of the auxiliary from **1.34** failed and a decarbonylated byproduct was formed. After deprotection of the THP group, the primary alcohol was selectively tosylated (**1.36**). The tosyl group was replaced by a phenylthio group and the remaining secondary alcohol was protected with PMB (**1.37**). Final oxidation of the sulfide **1.37** with *m*-CPBA afforded sulfone fragment **1.V**.

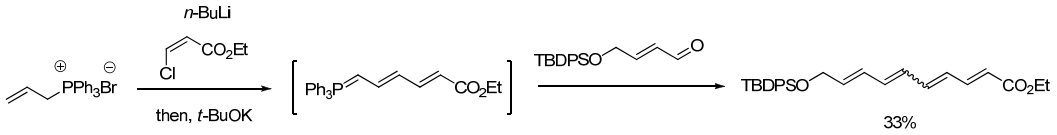


Key: (a) diphenyl carbonate, K_2CO_3; (b) *n*-BuLi, $CH_3CH_2C(O)Cl$; (c) Bu_2BOTf, Et_3N, Me_2CHCHO; (d) DHP, PPTS; (e) $LiAlH_4$; (f) MeOH, H^+; (g) TsCl, pyridine; (h) PhSNa; (i) PMBCl, KH; (j) *m*-CPBA

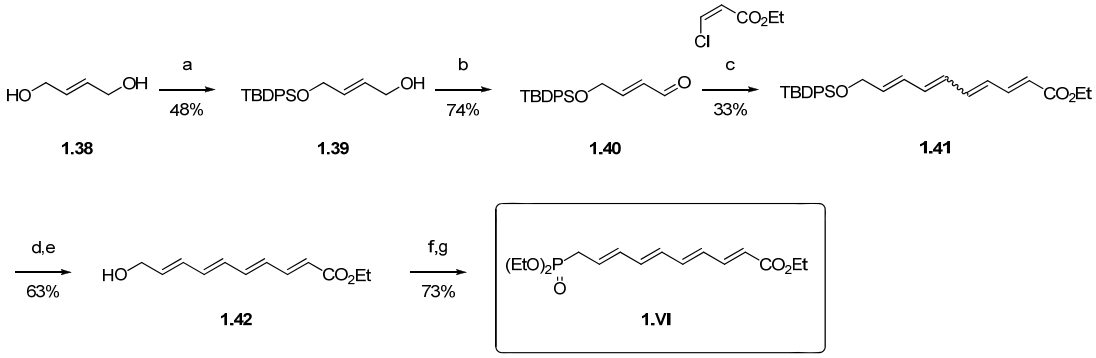
Scheme 1.8 Synthesis of sulfone fragment **1.V**.

1.3.3 Synthesis of tetraene phosphonate fragment 1.VI

Originally, Mory group attempted to use Hanessian's protocol for the synthesis of tetraene phosphonate **1.VI** (Scheme 1.9).[32] Due to the difficulty of C-C bond cleavage, they developed their own sequence of synthesizing fragment **1.VI**. Diol **1.38** was monoprotected with TBDPSCl in 48% yield. After oxidation of alcohol **1.39** with MnO_2, Wittig reaction with Vedejs reagent[33] was conducted to produce unstable tetraene ester **1.41** as a mixture of *E* and *Z* isomers. Silyl deprotection with Bu_4NF and photochemical isomerization generated all-*trans* tetraene alcohol **1.42** in 63% yield. Finally, bromination with PBr_3 and treatment with triethyl phosphate produced desired tetrahene phosphonate fragment **1.VI** in 73% yield (Scheme 1.10).



Scheme 1.9 Wittig reaction with Vedejs reagent.

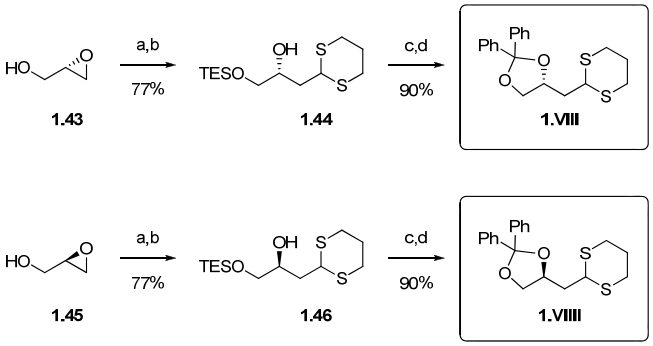


Key: (a) TBDPSCl, imidazole; (b) MnO_2; (c) allyl triphenylphosphonium bromide, *n*-BuLi, *t*-BuOK; (d) TBAF; (e) hv, I_2; (f) PBr_3; (g) $(OEt)_3P$

Scheme 1.10 Synthesis of tetraene phophonate fragment **1.VI**.

1.3.4 Synthesis of chiral building blocks 1.VIII, 1.VIIII and 1.X.

Fragments **1.VIII** and **1.VIIII** were synthesized from (*S*) and (*R*)-glycidol (**1.43** and **1.45**). The glycidols were protected with TESCl and the epoxides were opened with 2-lithio-1,3-dithiane, which gave the corresponding alcohols (**1.44** and **1.46**). Deprotection of the TES group and subsequent protection with benzophenone dimethyl ketal produced desired chiral building blocks **1.VIII** and **1.VIIII** (Scheme 1.11).

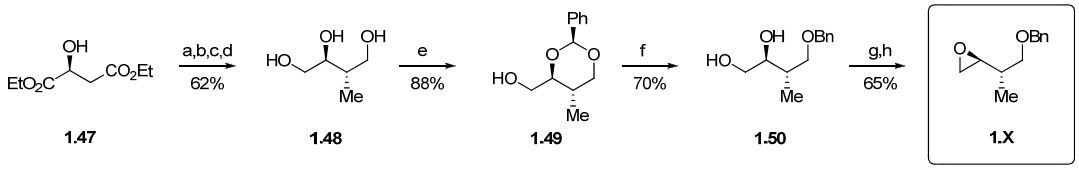


Key: (a) TESCl, Et_3N; (b) *n*-BuLi, 1,3-dithiane; (c) TBAF; (d) $Ph_2C(OMe)_2$

Scheme 1.11 Synthesis of chiral building blocks **1.VIII** and **VIIII**.

Chiral epoxide **1.X** was synthesized from (*S*)-diethyl malate **1.47** (Scheme 1.12). Methylation of **1.47** under the condition of Frater-Seebach methylation[16] followed by reduction with $LiAlH_4$ produced triol **1.48**.[34] Benzaldehyde dimethyl acetal protection generated the more favored six membered benzylidene product **1.49**. Regioselective reductive cleavage was conducted in the presence of DIBAL-H and desired ether **1.50** was successfully made in 70% yield. Finally, tosylation of the secondary alcohol and

treatment of the resulting product with *t*-BuOK generated chiral epoxide **1.X** in 65% yield.

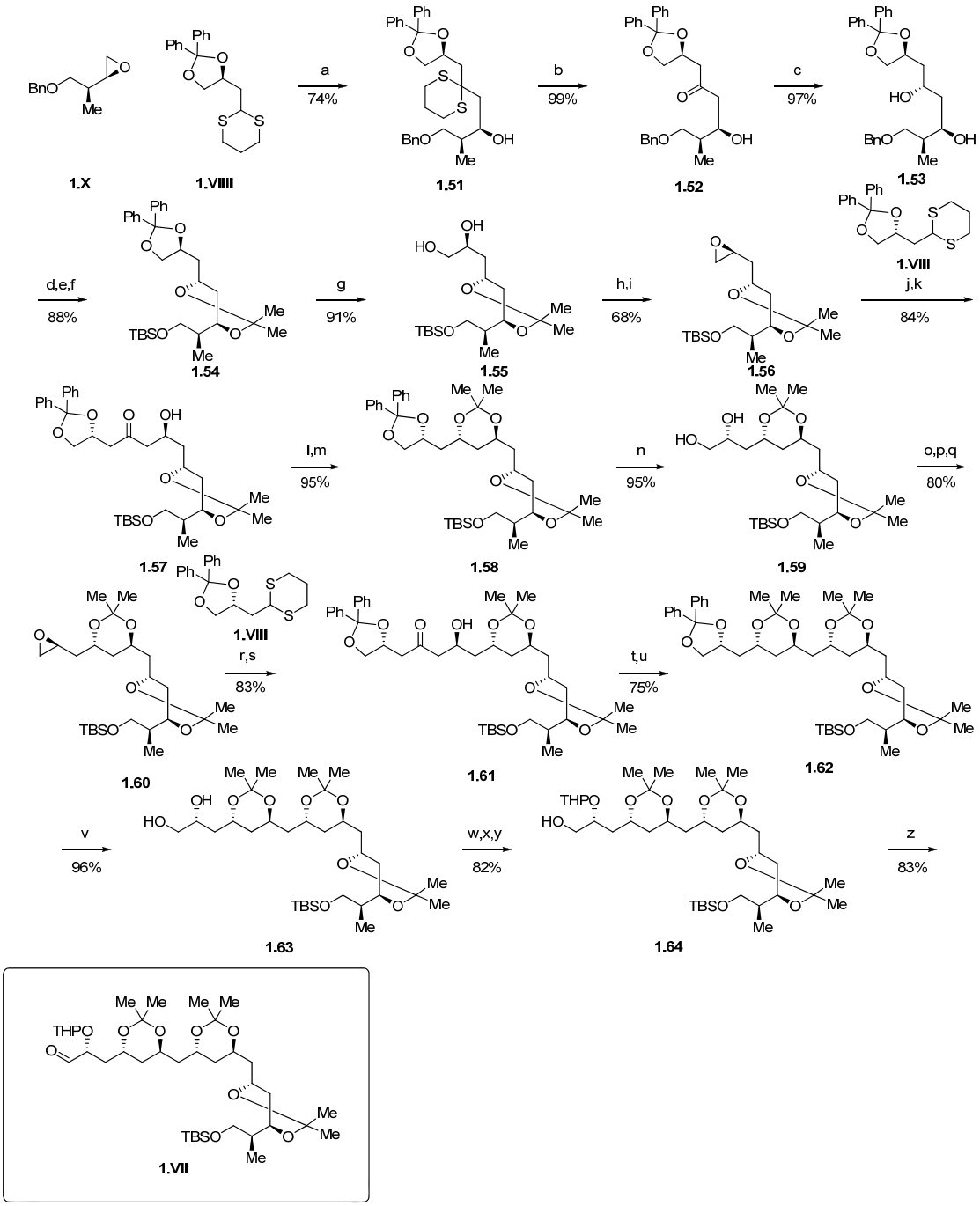


Key: (a) LDA, MeI; (b) DHP, PPTS; (c) $LiAlH_4$; (d) MeOH, H^+; (e) $PhCH(OMe)_2$, TsOH; (f) DIBAL; (g) TsCl, pyridine; (h) *t*-BuOK

Scheme 1.12 Synthesis of the chiral building block **1.X**.

1.3.5 Synthesis of fragment 1.VII.

Chiral epoxide **1.X** and dithiane **1.VIIII** were coupled with *n*-BuLi to generate alkylated dithiane **1.51** in 74% yield (Scheme 1.13). Treatment of the dithiane **1.51** with $Hg(ClO_4)_2$ in aqueous THF produced *β*-hydroxy ketone **1.52**, which was subjected to a diastereoselective reduction. *Syn*-diol **1.53** was generated in 97% yield with very high selectivity (s*yn*:*anti*=99.7:0.3) when ketone **1.52** was treated with $NaBH_4$ in the presence of Et_2BOMe. Acetonide protection of the diol and protecting group swap produced diphenylmethylene ketal **1.52**. It was necessary to change the protecting group from benzyl to TBS group because diphenylmethylene ketal group could be reductively cleaved in the later stage. The reductive cleavage was successfully conducted with Li and NH_3 to generate diol **1.55**. Chiral epoxide **1.56** was generated with the same condition of making chiral expoxide **1.X**. Similiar sequence of the reactions was conducted to generate chiral epoxide **1.60**. Alkylation followed by hydrolysis gave *β*-hydroxy ketone **1.57**. *Anti*-selective reduction was successfully conducted with $Me_4NBH(OAc)_3$ to produce the corresponding *anti*-diol in 95% yield with 97:3 diastereoselecivity.



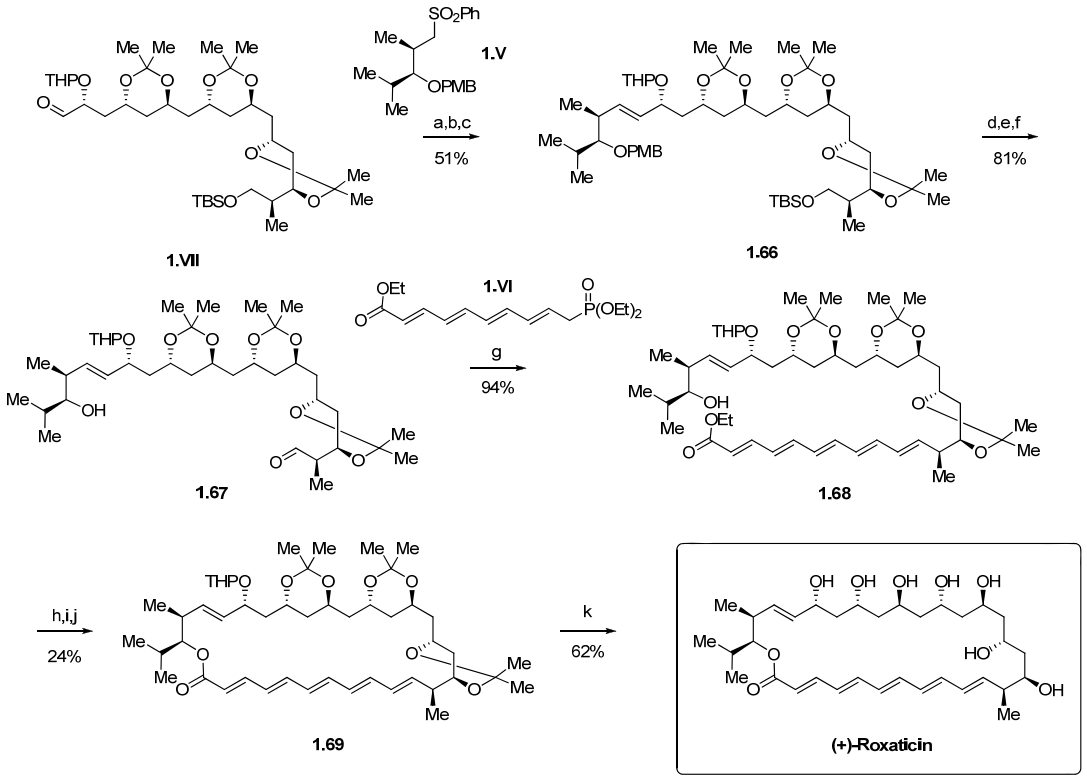
Key: (a) *n*-BuLi, THF; (b) $Hg(ClO_4)_2$; (c) $NaBH_4$, Et_2BOMe; (d) $Me_2C(OMe)_2$; (e) H_2, $Pd(OH)_2$; (f) TBSCl, imidazole; (g) Li, NH_3; (h) TsCl; (i) *t*-BuOK, Et_2O-MeOH; (j) **2**, *n*-BuLi, THF; (k) MeI, $CaCO_3$; (l) $Me_4NBH(OAc)_3$; (m) $Me_2C(OMe)_2$, PPTS; (n) Li, NH_3; (o) PivCl; (p) MsCl; (q) *t*-BuOK, Et_2O-MeOH; (r) *n*-BuLi; (s) MeI, $CaCO_3$; (t) $Me_4NBH(OAc)_3$; (u) $Me_2C(OMe)_2$, PPTS; (v) Li, NH_3; (w) PivCl, pyridine; (x) DHP, PPTS; (y) $LiAlH_4$; (z) SO_3pyr

Scheme 1.13 Synthesis of fragment **1.VII**.

Acetonide protection (**1.58**), diphenylmethylene group deprotection (**1.59**) and epoxidation gave chiral epoxide **1.60**. Again, alkylation with **1.VIII**, *anit*-selective reduction and deprotection gave diol **1.63**. Monoprotected product **1.64** was generated with the sequential protection group manipulation. The final oxidation of the primary alcohol produced fragment **1.VII**.

1.3.6 Endgame of (+)-roxaticin

Coupling reaction of fragments **1.VII** and **1.V** was conducted under Julia



(a) *n*-BuLi; (b) Ac_2O, pyridine; (c) Na-Hg; (d) TBAF; (e) Dess-Martin; (f) DDQ; (g) $LiN(TMS)_2$; (h) LiOH, THF, H_2O; (i) 2,4,6-trichlorobenzoyl chloride, Et_3N; (j) DMAP, toluene; (k) Dowex 50Wx8, MeOH

Scheme 1.14 Endgame of (+)-roxaticin.

olefination condition[30] to generate *trans*-disubstituted olefin **1.66** in 51% yield with 9:1 mixture of *E* and *Z* isomers (Scheme 1.14). TBS deprotection and subsequent oxidation gave a PMB protected aldehyde. The PMB group was successfully cleaved with DDQ to produce aldehyde **1.67**, which was then subjected to olefination reaction with **1.VI**. Aldehyde **1.67** was treated with the phosphonate anion generated *in situ* gave *seco*-ester **1.68** in 94% yield. Finally, the Yamaguchi method[28] modified by Yonemitsu[35] was conducted to generate macrolactone **1.69**. Global deprotection produced (+)-roxaticin.

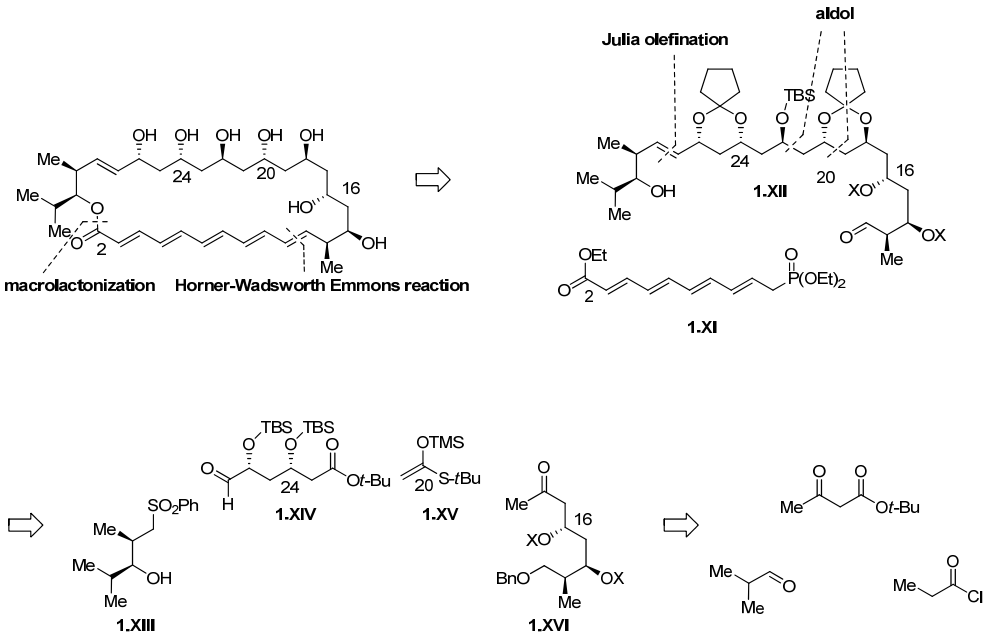
1.3.7 Summary

The synthesis was completed in 45 steps from (*S*)-diethyl malate (longest linear sequence), with a total number of 71 steps. Most of the stereogenic centers were constructed with diastereoselective reductions and Evans aldol reaction. The synthesis mainly depended on 1,3-polyol synthesis in an iterative fashion with four-carbon units. Interestingly, macrolactonization was conducted at the last stage of the synthesis using Yamaguchi method. This approach could be very useful for preparing analogous natural products.

1.4 SYNTHESIS OF (+)-ROXATICIN BY EVANS GROUP.

1.4.1. Synthetic plan

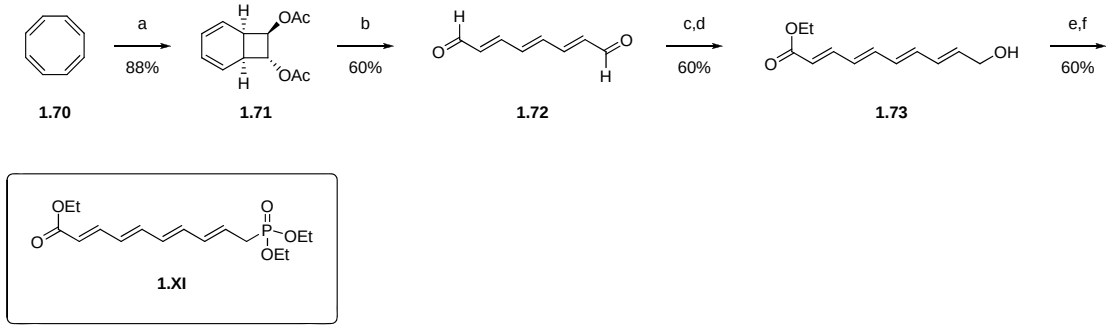
Evan synthesis[7e] also used the late stage introduction of oxo pentanes like Mory group synthesis,7[b,c,d] which led to two fragments **1.XI** and **1.XII**. The internal double bond was formed by Julia olefination.[30] C_{21}-C_{22} and C_{19}-C_{20} bonds were generated through aldol reaction, which gave four fragments, **1.XIII**, **1.XIV**, **1.XV** and **1.XVI**. Sulfone fragment **1.XIII** was constructed from isobutyaldehyde using asymmetric aldol reaction. Fragment **1.XIV** was formed under the addition of Chan's diene analogue to (benzyloxy)acetaldehyde. Ketone fragment **1.XVI** was generated by aldol and sequential homolgation reactions.



Scheme 1.15 Synthetic plan of (+)-roxaticin by Evans' group.

1.4.2 Synthesis of tetraene phosphonate fragment 1.XI

Evans group synthesized the polyene fragment **1.XI** in a single stereocontrolled step because most of other cases used repetitive and stepwise methods. This synthesis started with one-pot electrocyclic ring closure and Hg(II) mediated transacetylation reaction to produce compound **1.71** in 88% yield. Treatment of the compound **1.71** with $LiAlH_4$ and O_2 produced dialdehyde **1.72** through 2-electron oxidative ring fragmentation and olefin isomerization. Immediate treatment of **1.72** with sodium hydride and triethylphosphonacetate generated monoester-monoaldehyde, which was reduced with $NaBH_4$ to produce compound **1.73**. Allylic bromide was produced with $SOBr_2$, and a subsequent reaction with triethyl phosphate gave fragment **1.XI**.

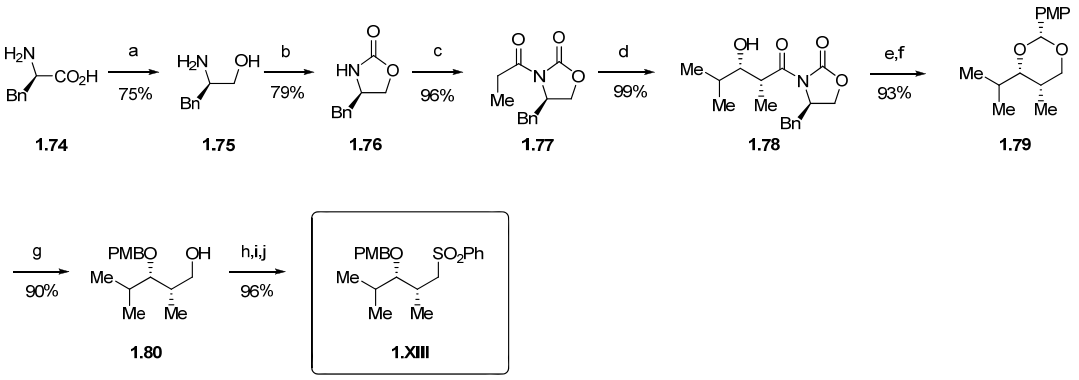


Key: (a) $Hg(OAc)_2$, AcOH; (b) $LiAlH_4$, THF, 0 ^oC to rt, then O_2; (c) triethylphosphonoacetate, NaH, -78 ^oC to rt, THF; (d) $NaBH_4$, EtOH; (e) $SOBr_2$, 2,6-di-*tert*-butylpyridine, -20 ^oC, THF; (f) $(EtO)_3P$, toluene, 110 ^{o} C

Scheme 1.16 Synthesis of tetraene phosphonate fragment **1.XI**.

1.4.3 Synthesis of sulfone fragment 1.XIII

Sulfone fragment **1.V** was synthesized from **1.74** with the Evan's auxiliary (Scheme 1.17).[31] Compound **1.77** was successfully coupled with isobutyraldehyde using boron-mediated aldol reaction to produce aldol product **1.78**. Cleavage of the auxiliary with $LiBH_4$ and protection provided *p*-anisaldehyde dimethylacetal **1.79**. Selective cleavage gave primary alcohol **1.80** with DIBAL-H, Mesylation, displacement of lithium thiophenylate, and with *m*-CPBA generated the sulfone fragment **1.XIII**. These three sequential steps were conducted without purification in 96% yield.

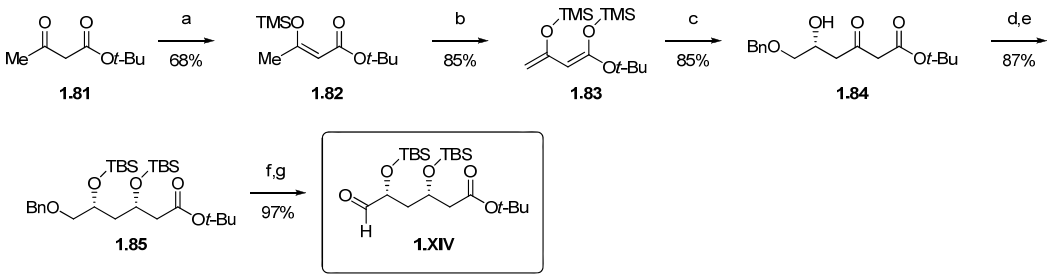


Key: (a) BF_3Et_2O, BH_3Me_2S, THF; (b) Et_2CO_3, K_2CO_3; (c) EtCOCl, BuLi, THF; (d) Bu_2BOTf, NEt_3, *i*-PrCHO, CH_2Cl_2, -78 °C, CH_2Cl_2; (e) $LiBH_4$, MeOH, THF, -78 °C; (f) cat. TsOH, *p*-MeOPhCH(OMe)$_2$, CH_2Cl_2; (g) DIBAl-H, CH_2Cl_2, -78 °C; (h) MsCl, NEt_3, CH_2Cl_2; (i) PhSLi, THF, -78 °C to 23 °C; (j) *m*-CPBA, CH_2Cl_2 $Zn(OTf)_2$;

Scheme 1.17 Synthesis of sulfone fragment **1.XIII**.

1.4.4 Synthesis of fragment 1.XIV

Fragment **1.XIV** began with the coupling of Chan's diene analogue **1.83** and (benyloxy)acetaldehyde using [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ as catalyst (Scheme 1.18). The corresponding product **1.84** was reduced with Et_2BOMe and $NaBH_4$ to generate *syn*-diol, which was bis-protected with TBS groups. Under the hydrogenation condition with Pd, the unprotected primary alcohol from **1.85** was afforded. Final oxidation gave fragment **1.XIV**.



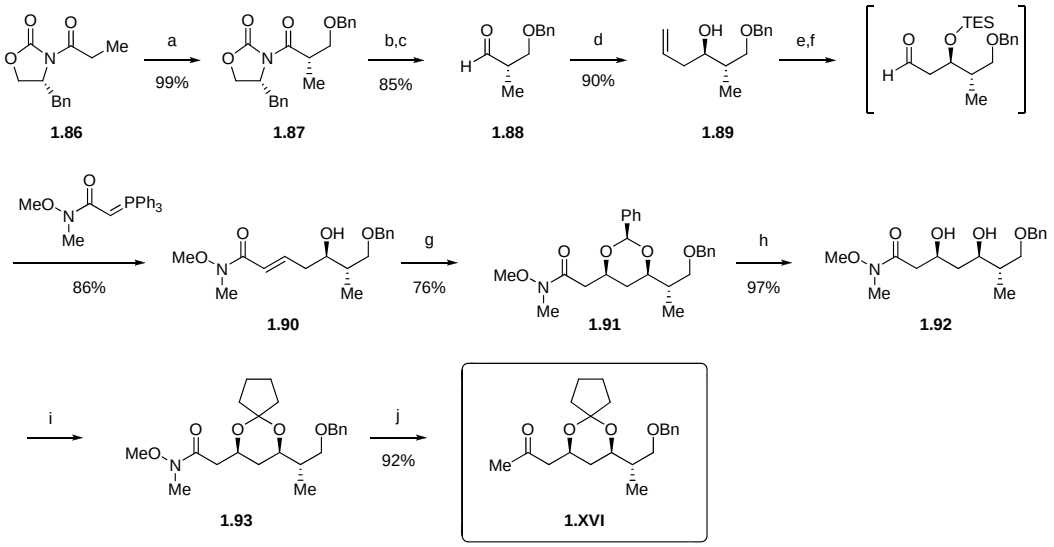
Key: (a) Et_3N, TMSCl, hexanes; (b) LDA, TMSCl, THF; (c) [Cu((S,S)-Ph-pybox)]$(SbF_6)_2$ (2 mol%), benzyloxyacetaldehyde, 99%ee; (d) Et_2BOMe, $NaBH_4$, MeOH, THF, -78 °C; (e) TBSCl, imidazole, CH_2Cl_2; (f) 2000 psi H_2, 10% Pd/C, EtOAc; (g) Dess-Martin, CH_2Cl_2

Scheme 1.18 Synthesis of fragment **1.XIV**.

1.4.5 Synthesis of ketone fragment 1.XVI

The synthesis of ketone fragment **1.XVI** began with Evans auxiliary chemistry. Asymmetric aldol reaction using titanium enolate generated from propionyl oxazolidinone **1.86** afforded **1.87**, which was then subjected to auxiliary cleavage with $LiBH_4$, followed by oxidation to give chiral aldehyde **1.88** (Scheme 1.19). This sequence

of reactions provided large quantities of enantiomerically pure aldehyde **1.88** in 85% yield over three steps. Keck's allylation method[36] was adopted for constructing homoallylic alcohol **1.89**. This chelation-cotrolled allylation provided 35:1 *anti*-diastereoseletivity in 90% yield. TES protection followed by ozonolysis provided aldehyde intermediate that was subjected to homologation with *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene) acetamide to generate amide **1.90** in 86% yield. Intramolecular hemiacetal conjugate addition of amide **1.90** produced *syn*-protected actetal **1.91** with benzaldehyde in the presence of catalytic amount of KHMDS. The benzylidene acetal was converted to cyclopentylidene ketal (**1.93**) because of its



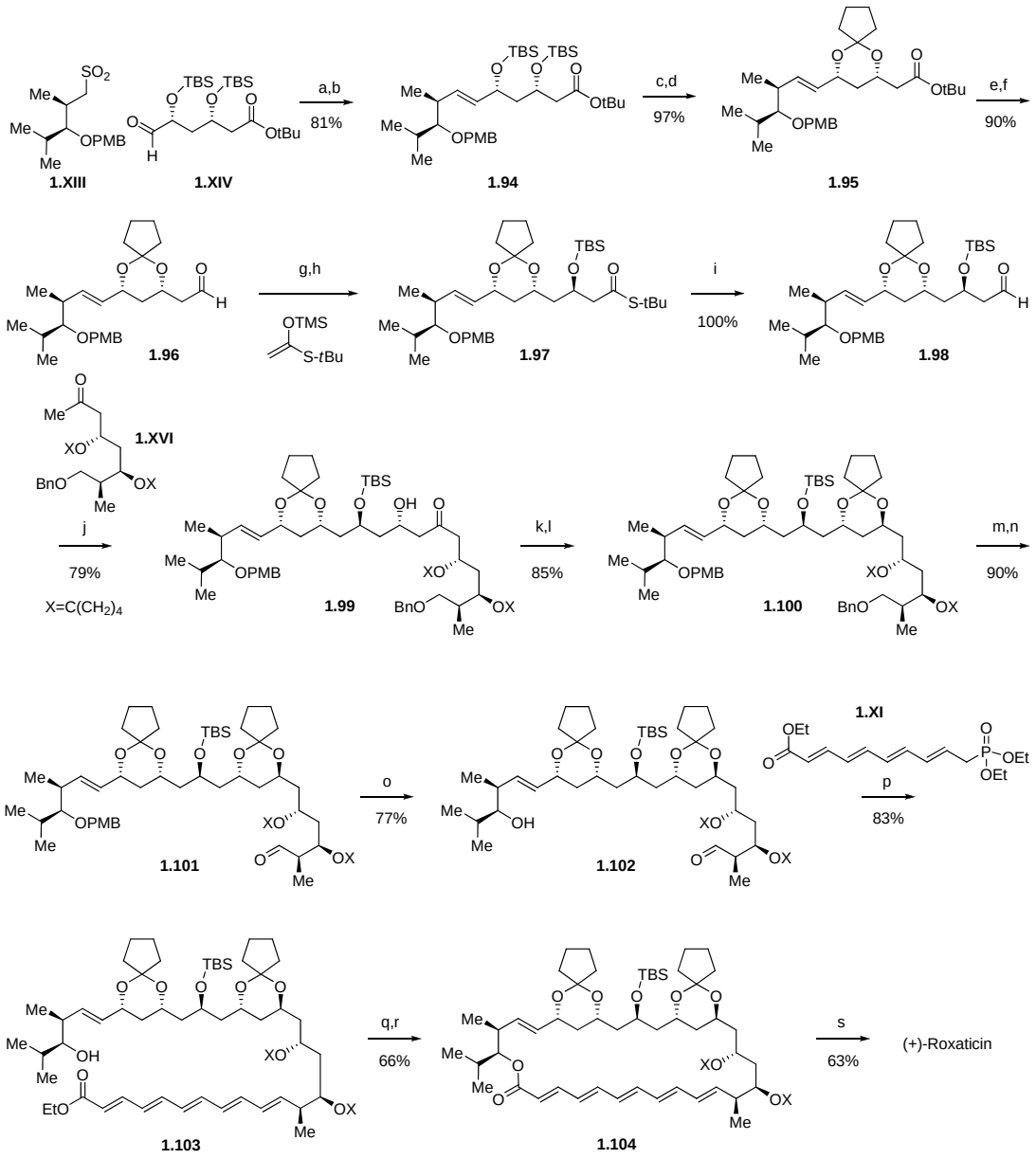
Key: (a) $TiCl_4$, NEt_3, $BnOCH_2Cl$, 0 ^oC, CH_2Cl_2; (b) $LiBH_4$, 0 ^oC, THF; (c) SO_3·pyr, DMSO, -10 ^oC, CH_2Cl_2; (d) allyltributyltin, $SnCl_4$, -78 ^oC, CH_2Cl_2; (e) TESCl, imidazole, CH_2Cl_2; (f) O_3, Ph_3P, N-MeO-N-Me(triphenylphosphoranylidene)-acetamide, TsOH, CH_2Cl_2; (g) cat. KHMDS, PhCHO, 0 ^oC, THF; (h) $Zn(OTf)_2$, EtSH, $NaHCO_3$, CH_2Cl_2; (i) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (j) MeLi, -78 ^oC, THF

Scheme 1.19 Synthesis of ketone fragment **1.XVI**.

incompatibility of reductive reaction at the later stage. Final treatment with MeLi provided desired ketone fragment **1.XVI** in 92% yield.[37]

1.4.6 Endgame of (+)-roxaticin

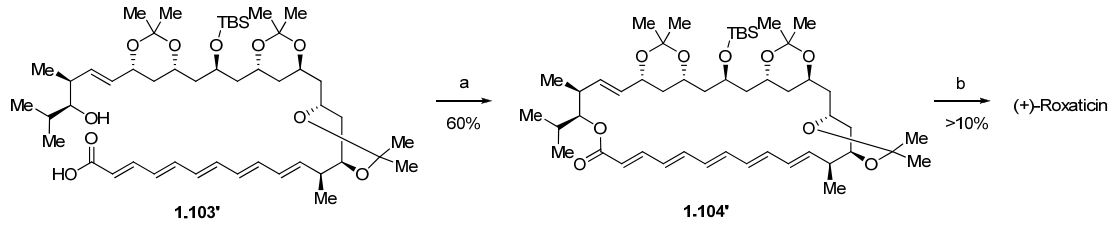
The synthesis of roxaticin began with the coupling reaction of fragments **1.XIII** and **1.XIV** (Scheme 1.20). Deprotonation of the sulfone **1.XIII** with *n*-BuLi and subsequent addition of BF_3•OEt_2 and aldehyde **1.XIV** afforded *β*-hydroxy sulfones.[30] Treatment with Na/Hg amalgam in buffered methanol generated *E*-olefin **1.94**. TBS ether protection groups were exchanged with cyclopentylidene ketal group (**1.95**) for better selectivity at the later stage of the synthesis. Upon oxidation state manipulation, aldehyde **1.96** was generated and was subjected to aldol reaction. Diastereoselecivity of the reaction was 5-7:1 With BF_3•OEt_2 and the mixture was protected with TBS group to give thioester **1.97**. Reduction with DIBAL-H and aldol reaction with fragment **1.XVI** gave aldol product **1.99** in 79% yield as a single isomer. Subsequent reduction was performed with $Me_4NHB(OAc)$, at -35 °C to produce the corresponding *anti*-diol as a single isomer. After protection with cyclopentylidene ketal (**1.100**), the benzyl group was reductively cleaved with LiDBB to generate the primary alcohol, which was oxidized under Dess-Martin oxidation condition (**1.101**). The PMB group was successfully cleaved with DDQ to produce substrate **1.102** for the olefination reaction with **1.XI**. Treatment of aldehyde **1.102** with the phosphonate anion generated *in situ* by LiHMDS gave the seco-ester **1.103** in 83% yield. Yamaguchi latonization[28] provided the macrolactone **1.104** in 66% yield. Global deprotection with PPTS gave (+)-roxaticin. Acetonide protected compound



Key: (a) *n*-BuLi, BF_3OEt_2, -78 °C, THF; (b) Na/Hg, Na_2HPO_4, -40 °C to 23 °C, MeOH; (c) HFpyr, THF; (d) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (e) $LiAlH_4$, THF; (f) Dess-Martin, CH_2Cl_2; (g) BF_3OEt_2, -90 °C, toluene; (h) TBSOTf, 2,6-lutidine, -78 °C, CH_2Cl_2; (i) DIBAl-H, -78 °C, toluene; (j) BuBOTf, NEt_3, -78 °C to 100 °C, Et_2O; (k) $Me_4NBH(OAc)_3$, -25 °C, CH_3CN, AcOH; (l) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (m) LiDBB, -78 °C, THF; (n) Dess-Martin, CH_2Cl_2; (o) DDQ, H_2O, CH_2Cl_2; (p) **3**, LiHMDS, -78 °C, THF; (q) LiOH, THF, H_2O, MeOH; (r) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, 23 °C, toluene; (s) PPTS, MeOH

Scheme 1.20 Endgame of (+)-roxaticin.

1.103' needed more harsh condition than cyclopentylidene ketals **1.103** to affore the corresponding cyclized compound **1.104'** (Scheme 1.21). More significantly, deproteciton of the acetonide gave only less than 10% yield of the natural product.



Key: (a) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, reflux, toluene; (b) H^+

Scheme 1.21 Synthesis of (+)-roxaticin from acetonide protected acid **1.103'**.

1.4.7 Summary

The synthesis was completed in 29 steps from (*L*)-phenyl alanine (longest linear sequence), with a total number of 52 steps. Most of the stereogenic centers were constructed by asymmetric aldol reactions using chiral auxiliaries. In this synthesis, new approach of generating the polyene fragment was illustrated. Among the previous syntheses of the roxaticin, this approach afforded the shortest synthesis.

Chapter 2 Rhodium-Catalyzed Aldol Coupling Reaction under Hydrogenation Condition

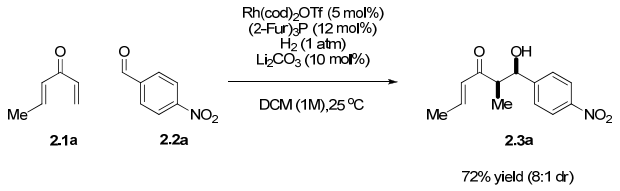
2.1 Reductive Aldol coupling of Divinyl ketones via rhodium-catalyzed hydrogenation

2.1.1 Background

Following seminal studies by Revis (1987),[1a] the catalytic reductive coupling of *α,β*-unsaturated carbonyl compounds and aldehydes to form aldol products, termed the "reductive aldol reaction", has been the subject of intensive investigation. To date, catalysts for reductive aldol coupling based on rhodium,[1, 2] cobalt,[3] iridium,[4a] palladium,[4b] copper,[4c-g] and indium[4h] have been described. Further, highly diastereo-[1c,2e,3b-d,4e,h,i] and enantioselective[1d,g,h,4a,f,g] variants have been achieved. The majority of catalytic systems for reductive aldol coupling employ acrylate pronucleophiles in combination with hydrosilanes as the terminal reductant. Krische and coworkers have developed conditions for hydrogen-mediated reductive aldol coupling that are applicable to commercially available methyl and ethyl vinyl ketones (MVK and EVK).[2a,e] Furthermore, upon the use of cationic rhodium catalysts ligated by tri-2-furylphosphine, exceptionally high levels of *syn*-diastereo-selection are observed.[2e,5] Remarkably, under the conditions of hydrogen-mediated aldol coupling, functional groups borne by the aldehyde that are generally considered "hydrogen labile" (alkynes, alkenes, benzylic ethers, and nitroarenes) remain intact.[2e] These results support the feasibility of couplings involving vinyl ketones that incorporate unsaturated functional groups.

2.1.2 Reaction optimization

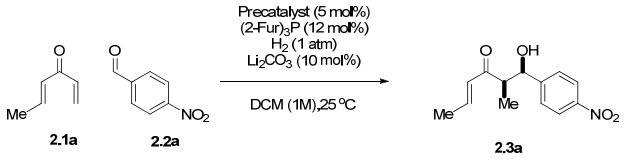
Our initial studies focused on the reductive coupling of crotyl vinyl ketone **2.1a** to *p*-nitrobenzaldehyde under our previously developed conditions for *syn*-selective aldol coupling.[2e] To our delight, crotyl vinyl ketone **2.1a** (200 mol%) was subjected to hydrogenation at ambient temperature and pressure in the presence of *p*-nitrobenzaldehyde **2.2a** (100 mol%) to furnish hydroxyenone **2.3a** in 72% isolated yield with an 8:1 *syn*/*anti* ratio (Scheme 2.1).



Scheme 2.1 reductive coupling of croty vinyl ketone to aldehyde.

In the hope of improving chemical yield and diastereoselectivity, solvent, reaction temperature and concentration were screened. Unfortunately the better reactivity and selectivity were not obtained. Finally, alternate rhodium precatalysts such as $Rh(cod)_2BARF$ (BARF=$[3,5\text{-}(CF_3)_2C_6H_3]_4B^-$), $Rh(cod)_2BF_4$ and $Rh(cod)_2SbF_6$ were screened. Upon use of $Rh(cod)_2BARF$, a substantial increase in diastereoselectivity is observed, but the isolated yield of hydroxyenone **2.3a** is diminished considerably (Table 2.1, entry 2). Similarly, upon use of $Rh(cod)_2BF_4$, a 61% isolated yield of coupling product **2.3a** is obtained with a 9:1 diastereomeric ratio (Table 2.1, entry 3). Gratifyingly, upon use of $Rh(cod)_2SbF_6$ as the precatalyst, hydroxyenone **2.3a** is produced in 82%

isolated yield with a 13:1 diastereomeric ratio, representing an improvement in both yield and stereoselectivity in comparison to the reaction employing $Rh(cod)_2OTf$ as the precatalyst (Table 2.1, entry 4).

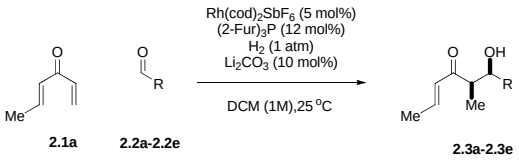


entry	rhodium precatalyst	yield (%)	dr (syn/anti)
1	$Rh(cod)_2OTf$	72	8:1
2	$Rh(cod)_2BARF$	55	17:1
3	$Rh(cod)_2BF_4$	61	9:1
4	$Rh(cod)_2SbF_6$	82	13:1

Table 2.1 Counterion effects in the hydrogen-mediated reductive aldol coupling of divinyl ketone **2.1a** to *p*-nitrobenzaldehyde **2.2a** employing cationic rhodium precatalyts.

Under optimized conditions using $Rh(cod)_2SbF_6$ as the precatalyst and $(2\text{-Fur})_3P$ as the ligand, the hydrogen-mediated aldol coupling of crotyl vinyl ketone **2.1a** to diverse aldehydes **2.2a-e** was conducted at ambient temperature and pressure (Table 2.2). High levels of *syn*-diastereoselection were observed using aromatic aldehydes (**2.3a**, 82% yield, 13:1 dr), α-heteroatom substituted aldehydes (**2.3b**, 80% yield, 9:1 dr; **2.3c**, 85% yield, 13:1 dr), heterocyclic aromatic aldehydes (**2.3d**, 94% yield, 11:1 dr), and α,β-unsaturated aldehydes (**2.3e**, 75% yield, 12:1 dr). Notably, the unsaturated products **2.3a-e** are not subject to overreduction under the conditions of hydrogen-mediated coupling due to a diminished rate of conjugate reduction in response to substitution of the enone moiety. Generally, reactions are complete within 7 h, as determined by consumption of the aldehyde. If the couplings are allowed to continue beyond this point, product

overreduction becomes evident. As a control experiment, hex-4-en-3-one and *p*-nitrobenzaldehyde were exposed to standard coupling conditions, and aldol addition product **2.3a** was not formed. Finally, upon reexposure of aldol addition product **2.3a** to standard coupling conditions, **2.3a** was recovered in high yield without any noticeable erosion in diastereoselectivity. This latter experiment suggests that hydrogen-mediated aldol addition is irreversible.



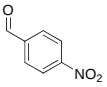
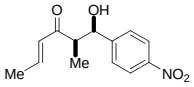
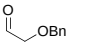
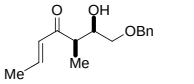
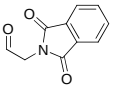
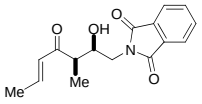
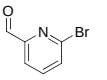
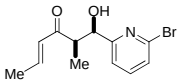
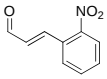
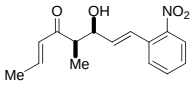
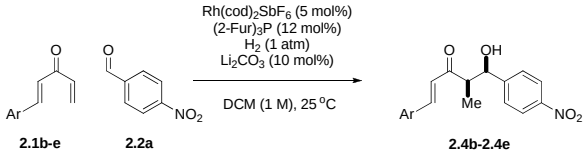
entry	aldehyde		product		yield (%)	dr (syn/anti)
1		2.2a		2.3a	82	13:1
2		2.2b		2.3b	80	9:1
3		2.2c		2.3c	85	13:1
4		2.2d		2.3d	94	13:1
5		2.2f		2.3f	75	12:1

Table 2.2 Hydrogen-mediated aldol coupling of crotyl vinyl enone **2.1a** to aldehydes **2.2a-e**.

As one would anticipate, crotyl vinyl ketone **2.1a** is somewhat unstable with respect to polymerization and must be used immediately upon isolation. Accordingly,

crystalline divinyl ketones of enhanced stability were sought, which led to the preparation of *para*-substituted styryl vinyl enones **2.1b-e**. With the exception of **2.1c**, these compounds are crystalline materials that may be stored for prolonged periods of time in the dark. To evaluate their reactivity in the reductive aldol coupling, styryl vinyl enones **2.1b-e** (150 mol %) were hydrogenated in the presence of *p*-nitrobenzaldehyde (100 mol %) at ambient temperature and pressure using $Rh(cod)_2SbF_6$ as the precatalyst (Table 2.3). As reflected by the isolated yield of aldol coupling products **2.4b-e**, it was found that the reaction responds remarkably to the effect of remote electron-withdrawing or -releasing groups. For example, whereas *para*-nitrostyryl vinyl enone **2.1b** provides only a 44% isolated yield of aldol coupling product **2.4b** (Table 2.3, entry 1), the corresponding *para*-(dimethylamino)styryl vinyl enone **2.1e** furnishes aldol coupling product **2.4e** in 93% yield under identical coupling conditions (Table 2.3, entry 4). These effects may be attributed to modulation of the HOMO energies of the intermediate rhodium enolates, with more reactive rhodium enolates being derived from precursors possessing electron-releasing *p*-styryl substituents. It is also interesting to note that diastereoselectivity decreases with increasing enolate reactivity, presumably due to intervention of boatlike transition structures, or increased isomerization of enolate geometry in advance of aldol coupling. As previously hypothesized,[2e] it is believed that *Z*-(*O*)-enolate formation occurs with high levels of kinetic stereospecificity by way of internal hydride delivery to the enone s-*cis* conformer through a six-centered transition structure.[6] Addition of the Z-(*O*)-enolate to the aldehyde through a Zimmerman-Traxler-type transition structure would then account for the observed *syn*-diastereoselectivity.[7]



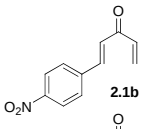
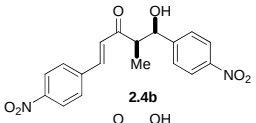
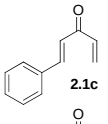
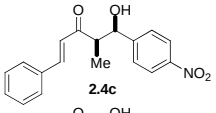
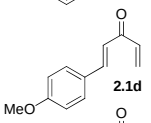
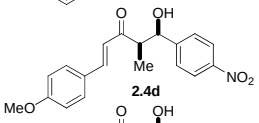
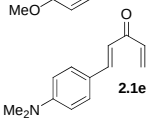
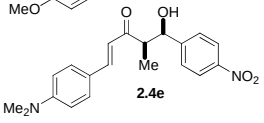
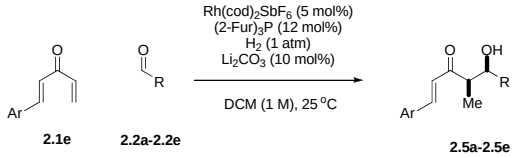
entry	styryl vinyl ketone	product	yield (%)	dr (syn/anti)
1	 **2.1b**	 **2.4b**	44	16:1
2	 **2.1c**	 **2.4c**	50	12:1
3	 **2.1d**	 **2.4d**	64	11:1
4	 **2.1e**	 **2.4e**	93	10:1

Table 2.3. Reductive aldol coupling of styryl vinyl ketones.

Under standard conditions using $Rh(cod)_2SbF_6$ as the catalyst precursor and Fur_3P as the ligand, the hydrogen- mediated aldol coupling of *para*-(dimethylamino)styryl vinyl ketone **2.1e** to aldehydes **2.2a-e** was conducted at ambient temperature and pressure (Table 2.4). Again, highly *syn*-diastereoselective coupling is observed for aromatic aldehydes (**2.5a**, 93% yield, 10:1 dr), α-heteroatom-substituted aldehydes (**2.5b**, 90% yield, 10:1 dr; **2. 5c**, 81% yield, 17:1 dr), heterocyclic aromatic aldehydes (**2.5d**, 87% yield, 11:1 dr), and α,β-unsaturated aldehydes (**2.5e**, 71% yield, 13:1 dr). Unlike adducts **2.3a-e**, the *para*-(dimethylamino)styryl containing adducts **2.5a-e** are far less susceptible to overreduction under the conditions of hydrogen-mediated C-C coupling. Additionally, for couplings that employ **2.1e**, lower loadings of a pronucleophile can be used.



2.1e **2.2a-2.2e** **2.5a-2.5e**

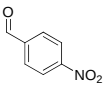
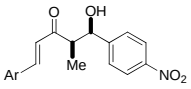
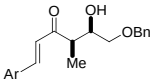
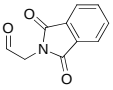
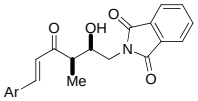
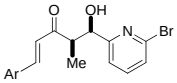
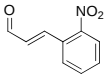
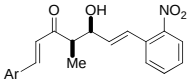
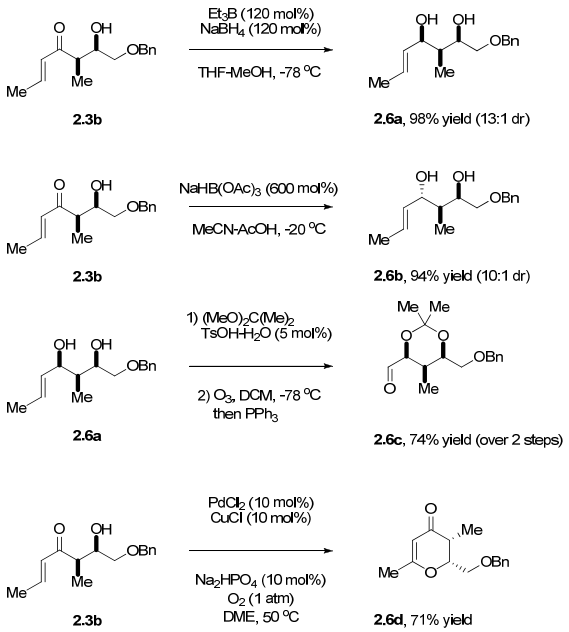
entry	aldehyde		product		yield (%)	dr (syn/anti)
1		2.2a		2.5a	93	10:1
2		2.2b		2.5b	90	10:1
3		2.2c		2.5c	81	17:1
4		2.2d		2.5d	87	11:1
5		2.2f		2.5f	71	13:1

Table 2.4 Hydrogen-mediated aldol coupling of styryl vinyl enone **2.1e** to aldehydes **2.2a-e** (Ar=*p*-Me_2NPh).

2.1.3 Application

To illustrate the relevance of this methodology with respect to the synthesis of polypropionate-derived substructures, aldol coupling product **2.3b** was subjected to several different transformations (Scheme 2.2). Exposure of **2.3b** to conditions for *syn*-diastereoselective hydroxy-directed reduction affords the *syn*-1,3-diol containing stereotriad **2.6a** with a diastereomeric ratio of 13:1.[8] Access to the corresponding *anti*-1,3-diol **2.6b** is achieved upon treatment of **2.3b** with $NaHB(OAc)_3$.[9] Here, a diastereomeric ratio of 10:1 is observed. As illustrated by the conversion of **2.6a** to **2.6c**,

the crotyl residue may serve as a masked aldehyde, enabling entry into higher polyols. Finally, oxidative cyclization catalyzed by palladium permits direct conversion of **2.3b** to dihydropyranone **2.6d**.[10]



Scheme 2.2 Elaboration of aldol adduct **2.3b** to diverse building blocks for polypropionate construction.

2.1.4 Summary

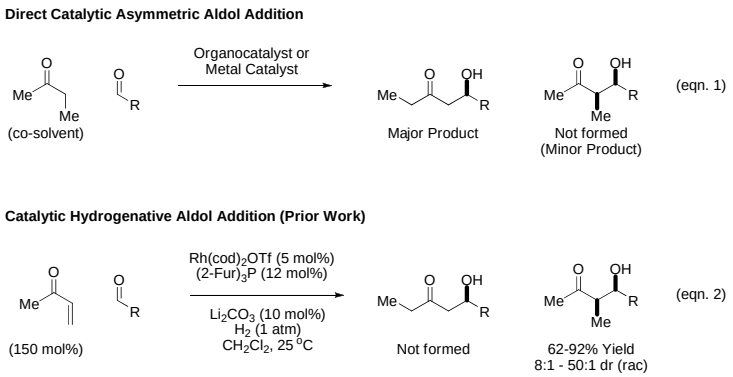
Rhodium-catalyzed hydrogenation of divinyl ketones **2.1a** and **2.1e** in the presence of aldehydes **2.2a-e** results in highly *syn*-diastereoselective reductive aldol coupling to afford the *α*,*β*-unsaturated coupling products **2.3a-e** and **2.5a-e**, respectively, without overreduction. As revealed by a survey of counterions ($Rh(cod)_2X$, where X = OTf, BF_4, SbF_6, BARF), $Rh(cod)_2SbF_6$ is identified as the optimum precatalyst for

reductive aldol couplings of this type. Finally, for *para*-substituted styryl vinyl ketones **2.1b-e**, a progressive increase in isolated yield in response to the presence of electron-releasing *para*-substituents is observed. These studies offer further insight into the structural and interactional features of the catalytic system required for efficient hydrogen-mediated aldol coupling and provide new methods for the construction of natural products that incorporate polypropionate motifs.

2.2 DIASTEREO- AND ENANTIOSELECTIVE HYDROGENATIVE ALDOL COUPLING OF VINYL KETONES

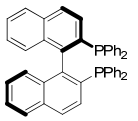
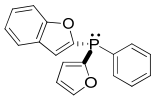
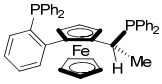
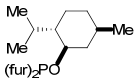
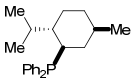
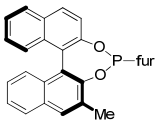
2.2.1 Background

The reductive coupling of α,β-unsaturated carbonyl compounds to aldehydes and ketones, termed the "reductive aldol reaction", has become the topic of intensive investigation.[11] Enantioselective reductive aldol couplings of vinyl ketones, such as methyl vinyl ketone (MVK), would enable access to branched aldol adducts, providing a regiochemical complement to direct organocatalytic and metal catalyzed aldol couplings of nonsymmetric ketones, such as 2-butanone, which furnish linear aldol adducts (eqn. 1).[12] In 2002, catalytic hydrogenation of vinyl ketones in the presence of aldehydes results in reductive aldol coupling to furnish branched aldol adducts as diastereomeric mixtures.[13a] Later (2006), it was found that high levels of *syn*-diastereoselectivity in hydrogen-mediated reductive aldol couplings of vinyl ketones are obtained through the use of tri-2-furylphosphine (Fur_3P) ligated rhodium catalysts (eqn. 2).[13b-d] However, to date, enantioselective reductive aldol couplings of vinyl ketones have not been devised.



2.2.2 Reaction optimization

The initial screen for the asymmetric reductive aldol reaction began with attempting to couple methyl vinyl ketone and aldehyde **2.7b** under hydrogenation condition with various chiral ligands (Table 2.5). As indicated in Table 2.5, most of the ligands showed low to moderate selectivity. Efforts toward enantioselective variants of such hydrogenative aldol couplings were especially challenging due to the fact that (a) only trace quantities of product are obtained using chelating phosphine ligands (Table 2.5, entry 1), (b) π-acidic ligands such as Fur_3P are required to enforce high levels of diastereoselection, yet (c) commercially available π-acidic chiral monodentate ligands, for

entry	Ligand	yield	d.r.	ee	entry	Ligand	yield	d.r.	ee
1		10%	3:1	27%	4		85%	18:1	6%
2		trace	-	-	5		80%	8:1	42%
3		trace	-	-	6		79%	8:1	43%

[a] Reactions were conducted by Dr. Cisco Bee and Dr. Hiroki Iida

Table 2.5 Asymmetric adol reaction under hydrogenation condition with various chiral ligands.

example, BINOL-derived phosphites and phosphoramidites, are presumably too π-acidic and provide only trace quantities of product.(Table 2.5, entry 4, 5 and 6)

To address the issue, the design, preparation and assay of novel chiral monodentate *P*-based ligands were undertaken. Over a period of years numerous ligands were assayed, yet those displaying promising levels of asymmetric induction were not amenable to facile and systematic structural variation. Hence, a versatile template enabling well-defined structure-selectivity trends was sought. TADDOL-like phosphonites[14] present three structural elements that may be independently optimized: (a) the *P*-aryl moiety (R_1), (b) the ketal substructure (R_3), and (c) the groups appended to the tertiary carbinol center (R_2). (Figure 2.1)

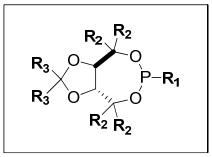
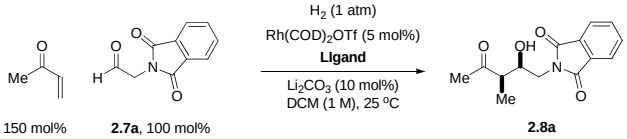
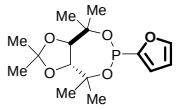
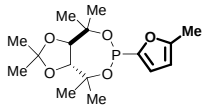
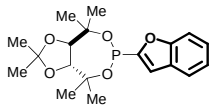
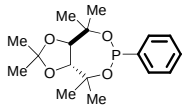
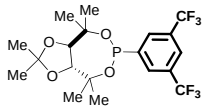


Figure 2.1 TADDOL-like phosphonite ligand.

Initially different *P*-aryl moieties (R_1) were screened while R_2 and R_3 were fixed as a methyl group (Table 2.6). Furyl substitution gave excellent reactivity (90% yield) and moderate selectivity (59% ee) (Table 2.6, entry 1). 2-methyl furyl gave only 52% product with poor selectivity (50% ee) (Table 2.6, entry 2). When the furyl group was changed to benzofuryl, product **2.8a** was produced with moderate reactivity (64% yield) and good selectivity (66% ee) (Table 2.6, entry 3). Installation of a phenyl group at this



150 mol% **2.7a**, 100 mol% **2.8a**

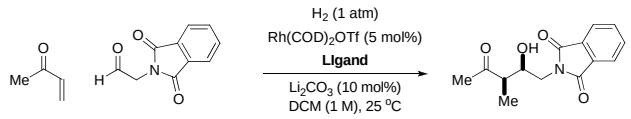
entry	Ligand	yield (%)	%ee
1[a]		90	59
2[a]		52	50
3		64	66
4		20	80
5[a]		30	45

[a] conducted by Dr. Cisco Bee

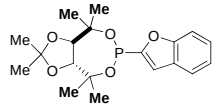
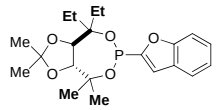
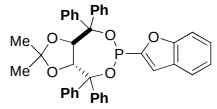
Table 2.6 Screen for R_1 group of TADDOL-like phosphonites ligands.

position gave very high selectivity (80% ee) but poor reactivity (20% yield) (Table 2.6, entry 4).

Having set the benzofuryl group as R_1, R_2 group was investigated. Changing R_2 group from methyl to ethyl and even phenyl group resulted in poor reactivity with 32% and 15% yield, respectively. Methyl was used since evne though ethyl gives good selectivity (75% ee), reactivity (32% yield) is poor (Table 2.7).



150 mol% **2.7a**, 100 mol% **2.8a**

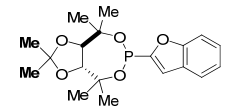
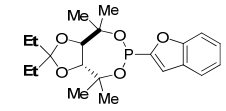
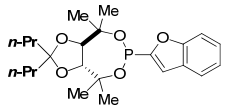
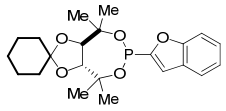
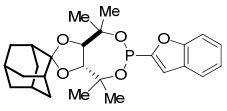
entry	Ligand	yield (%)	%ee
1		64	66
2		32	76
3[a]		15	30

[a] conducted by Dr. Cisco Bee

Table 2.7 R_2 group screen in synthesis of TADDOL-like phosphonite ligands.

Finally, the ketal substructure (R_3) groups were tested. When the size of the group is increased from methyl to ethyl, the selectivity (75% ee) and reactivitiy (75% yield) were increased (Table 2.8, entry 2). However, further increasing to *n*-propyl group did not help to increase the reactivity and selectivity (Table 2.8, entry 3). Cyclic ketals such as cyclohexyl group improved the yield of product (90%) but only moderate selectivity (56% ee) was observed (Table 2.8, entry 4). Adamantyl group also displayed only moderate reactivity and selectivity (Table 2.8, entry 5). Based on the results, ethyl group was established as R_3 group.

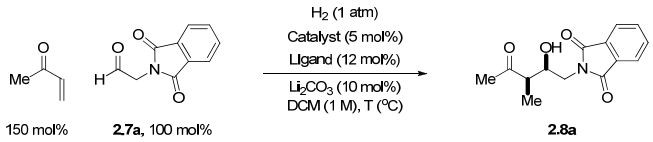
150 mol% **2.7a,** 100 mol% **2.8a**

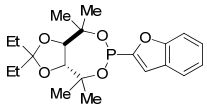
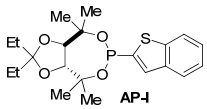
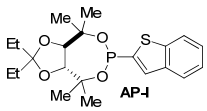
entry	Ligand	yield (%)	%ee
1		64	66
2		75	75
3[a]		76	69
4[a]		90	56
5		73	57

[a] conducted by Dr. Cisco Bee

Table 2.8 Screen for R_3 group of TADDOL-like phosphonite ligands.

Gratifyingly further screens of R_1 group revealed a benzothiophene group gave better results than benzofuran (Table 2.9, entry 2). Lowering the reaction temperature also helped to increase the reactivity and selectivity (Table 2.9, entry 3). Optimal efficiencies and selectivities were observed using the preformed **Rh complex I** derived from $Rh(cod)_2OTf$ and benzothiphene substituted ligand **AP-I** as a precatalyst. Under these reaction conditions, aldehyde **2.7a** is transformed to the *syn*-aldol **2.8a** with exceptional levels of relative and absolute stereocontrol (Table 2.9, entry 4).

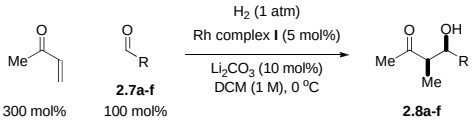


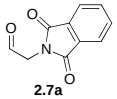
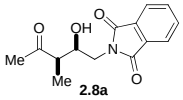
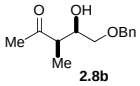
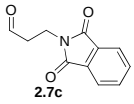
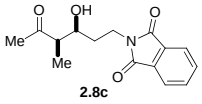
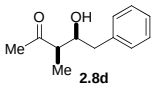
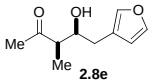
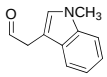
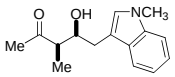
entry	Catalyst	Ligand	T (°C)	yield (%)	%ee
1	$Rh(cod)_2OTf$		25	75	75
2[a]	$Rh(cod)_2OTf$	 AP-I	25	90	92
3	$Rh(cod)_2OTf$	 AP-I	0	94	94
4	**$[Rh(cod)(AP\text{-}I)_2]OTf$**		0	88	96

[a] conducted by Abbas Hassan

Table 2.9 Optimization of asymmetric hydrogenative aldol reaction.

The scope of the preformed AP-I ligated **Rh complex I** was examined in reductive aldol couplings of MVK to diverse aldehydes. Beyond aldehyde **2.7a**, benzyl protected aldehyde **2.7b** (Table 2.10, entry 2), β-heteroatom substituted aldehyde **2.7c** (Table 2.10, entry 3) and α-(hetero)aryl aldehydes **2.7d**, **2.7e**, and **2.7f** (Table 2.10, entry 4, 5 and 6) were found to engage in highly diastereo- and enantioselective hydrogenative aldol additions.

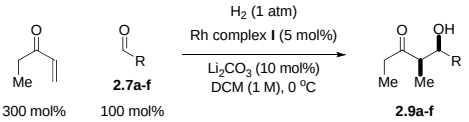


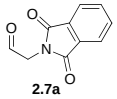
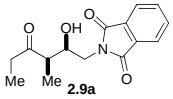
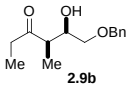
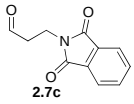
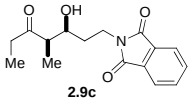
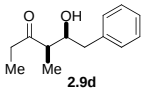
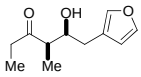
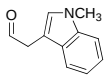
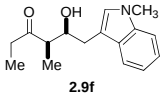
entry	aldehyde	product	yield (%)	dr	%ee
1[a]	 **2.7a**	 **2.8a**	88	50:1	96
2	 **2.7b**	 **2.8b**	85	25:1	91
3[a]	 **2.7c**	 **2.8c**	88	50:1	85
4	 **2.7d**	 **2.8d**	70	25:1	90
5	 **2.7e**	 **2.8e**	79	11:1	87
6[b]	 **2.7f**	 **2.8f**	92	15:1	87

[a] conducted by Dr. Cisco Bee, [b] conducted by Abbas Hassan

Table 2.10 Diastereo- and enantioselective aldol coupling of methyl vinyl ketone to aldehdes **2.7a**-**f**.

An identical set of aldehydes were tested with ethyl vinyl ketone under the hydrogenation condition. Generally, slightly better reactivity but similar selectivity were observed (Table 2.11)

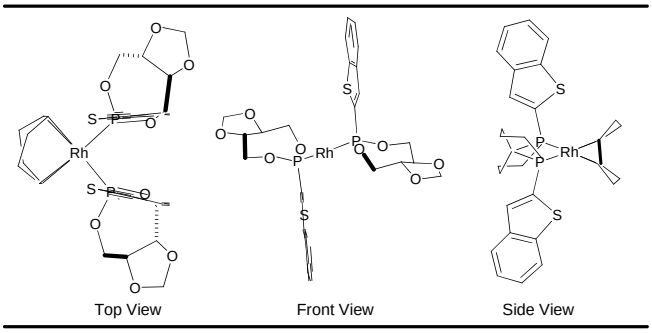


entry	aldehyde	product	yield (%)	dr	%ee
1[a]	 **2.7a**	 **2.9a**	94	45:1	94
2	 **2.7b**	 **2.9b**	96	21:1	88
3[a]	 **2.7c**	 **2.9c**	96	25:1	92
4	 **2.7d**	 **2.9d**	76	22:1	90
5	 **2.7e**	 **2.9e**	83	25:1	88
6[b]	 **2.7f**	 **2.9f**	97	25:1	90

[a] conducted by Dr. Cisco Bee, [b] conducted by Abbas Hassan

Table 2.11 Diastereo- and enantioselective aldol coupling of ethyl vinyl ketone to aldehdes **2.7a-f**.

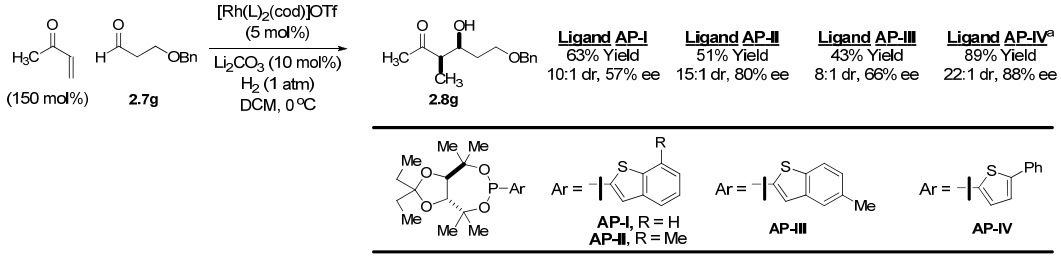
Single crystal X-ray diffraction analysis of $[Rh(cod)(L)_2]OTf$ (L = the acetonide of AP-I) reveals a C_2-symmetric arrangement around Rh (Figure 2.2). Based upon the hypothesis that a similar metal-ligand arrangement is evident in the stereo-determining event, ligands AP-II and AP-IV were also designed. For ligands AP-II and AP-IV the (benzo)thiophene moiety is substituted such that the purported chiral pocket is deepened,



[a]The figure graphics are depictions of crystallographic data imported into ChemDraw Ultra 9.0. For clarity, the following substructures were omitted. Top: The methyl groups and triflate ion. Front: The methyl groups, triflate ion and 1,5-cyclooctadiene. Side: The methyl groups, triflate ion, dioxolane rings and phosphonite oxygen atoms

Figure 2.2 Structure of $[Rh(cod)(L)_2]OTf$ (L = the acetonide analogue of AP-I) determined by X-ray diffraction reveals C_2-symmetric arrangement.

thus potentially conferring heightened levels of enantioselection. The veracity of this analysis is supported by the fact that AP-II and AP-IV are both found to induce higher levels of optical enrichment, whereas AP-III, which projects the methyl residue into an inactive volume of space, displays selectivities comparable to those of AP-I (Table 2.12).



[a] conducted by Abbas Hassan

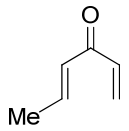
Table 2.12 Enantioselective aldol coupling of MVK to $BnO(CH_2)_2CHO$ using ligands AP-I, AP-II, AP-III and AP-IV.

2.2.3 Summary

In summary, we report the first enantioselective reductive aldol coupling of vinyl ketones, which were achieved through the design of an effective new class of TADDOL-like phosphonite ligands. This study further demonstrates that organometallics arising transiently in the course of catalytic hydrogenation offer a byproduct free alternative to preformed organometallic reagents, for example enol(ate) derivatives, employed routinely in classical carbonyl addition processes.

2.3 EXPERIMENTAL SECTION

Hexa-1,4-dien-3-one

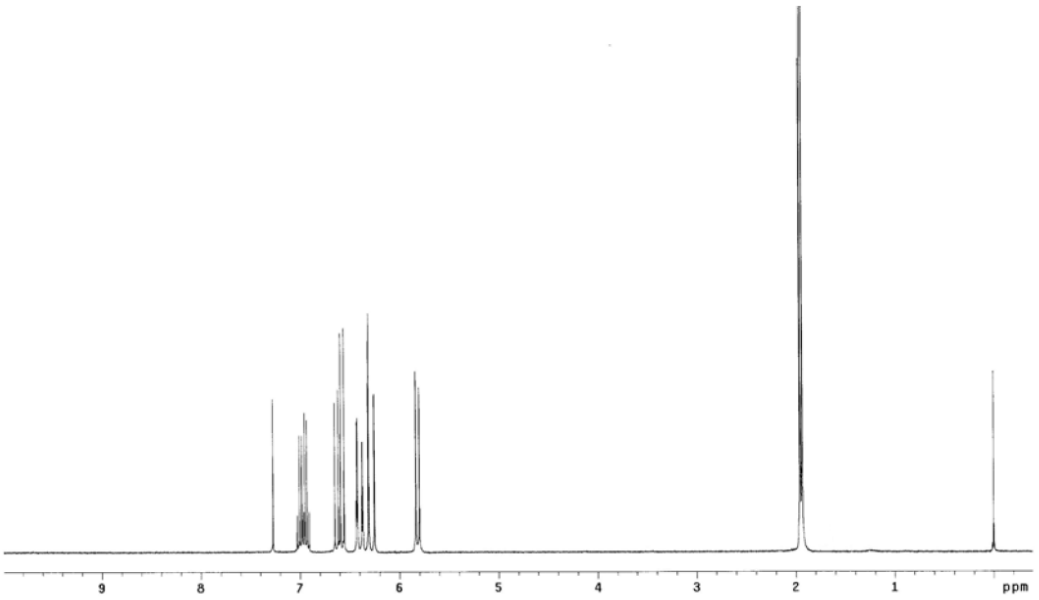


2.1a

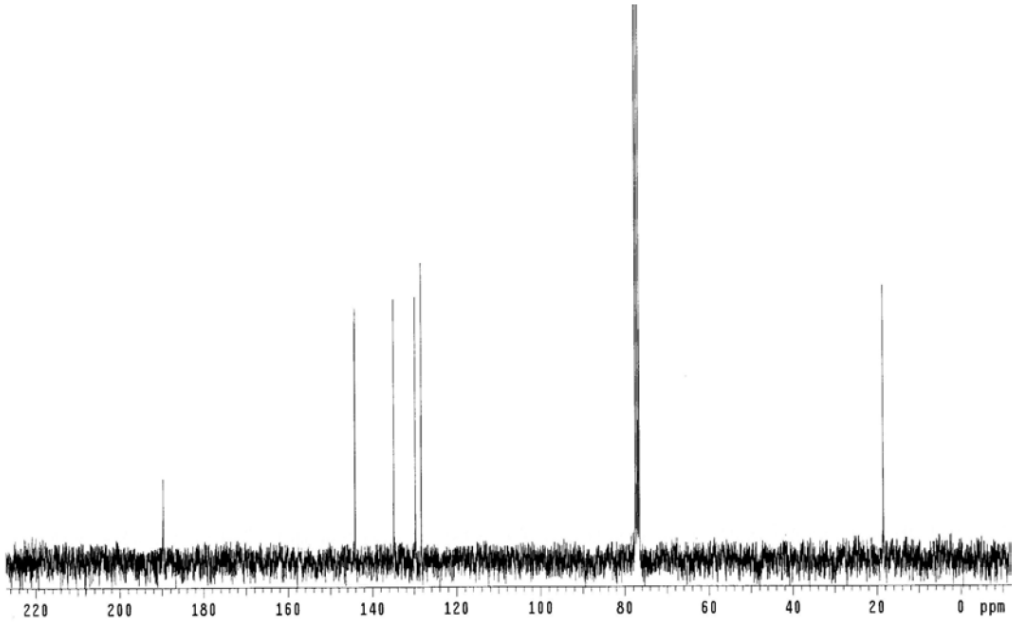
To a solution of hexa-1,4-dien-3-ol (1.0 g, 10.2 mmol, 100 mol%) in CH_2Cl_2 (50 mL) at 0 ^oC was added MnO_2 (8.86 g, 101.9 mmol, 999 mol%). The reaction mixture was allowed to stir for 12 hours at ambient temperature, at which point the reaction mixture was filtered through a pad of celite with the aid of Et_2O. The resulting solution was evaporated and the residue was purified by flash chromatography (SiO_2: Et_2O/pentane) to afford the title compound (380 mg, 3.95 mmol) as a viscous yellow solid (39 % yield).

TLC: R_f 0.3 (Et_2O/pentane, 1/10). ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (dq, J = 15.6, 6.9 Hz, 1H), 6.60 (dd, J = 17.4, 10.5 Hz, 1H), 6.40 (dq, J = 15.6, 1.8 Hz, 1H), 6.28 (dd, J = 17.4, 1.5 Hz, 1H), 5.82 (dd, J = 10.5, 1.5 Hz, 1H), 1.95 (dd, J = 6.9, 1.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 144.1, 134.8, 129.7, 128.3, 18.5. HRMS Calcd. for C_6H_8O (M+1): 97.0653, Found: 97.0653. FTIR (NaCl film): 1666, 1635, 1611, 1443, 1403, 1276, 1216, 1135, 1090, 966, 749 cm^{-1}.

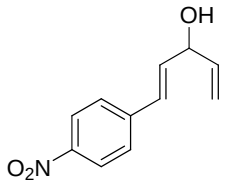
^{1}H NMR



^{13}C NMR



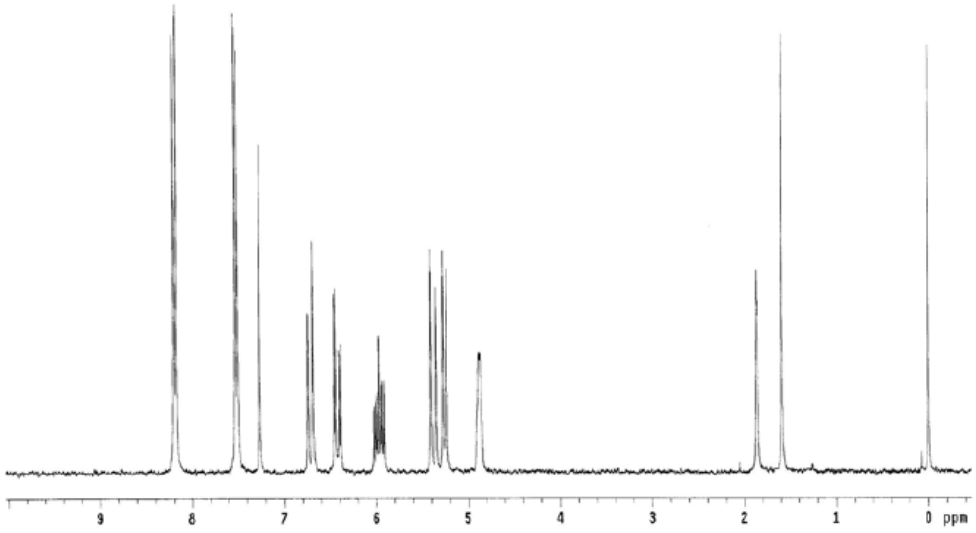
1-(4-Nitro-phenyl)-penta-1,4-diene-3-ol



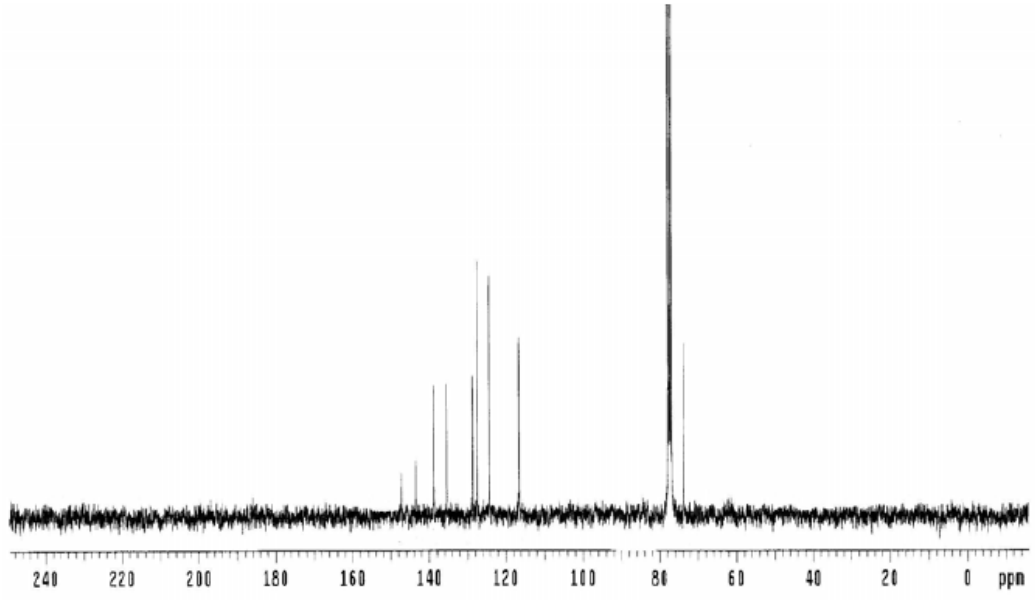
To a solution of vinylmagnesium bromide (1.0 M in THF, 25.6 mL, 25.6 mmol, 113 mol%) was added a solution of 3-(4-nitro-phenyl)-propenal (4.0 g, 22.6 mmol, 100 mol%) in THF (25 mL) at -78 ^{o}C. The reaction mixture was allowed to stir for 2 hours at ambient temperature, at which point the reaction mixture was cooled to 0 ^{o}C and saturated NH_4Cl (aq.) was added. The reaction mixture was extracted with Et_2O (3 times). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (3.33 g, 16.2 mmol) as a yellow solid (72 % yield).

TLC: R_f 0.4 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20-8.17 (m, 2H), 7.53-7.50 (m, 2H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.42 (dd, *J* = 15.9, 5.7 Hz, 1H), 5.97 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H). 4.88 (ddd, *J* = 6.0, 5.7, 3.6 Hz, 1H), 1.86 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 143.4, 138.8, 135.4, 128.5, 127.3, 124.3, 116.6, 73.7. HRMS Calcd. for $C_{11}H_{11}NO_3$ (M+1): 206.0817, Found: 206.0816. FTIR (NaCl film): 3384, 1595, 1513, 1343, 1109, 971, 928, 860, 748 cm^{-1}. M.P.: 50-51 ^{o}C.

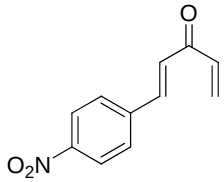
^{1}H NMR



^{13}C NMR



1-(4-Nitro-phenyl)-penta-1,4-dien-3-one

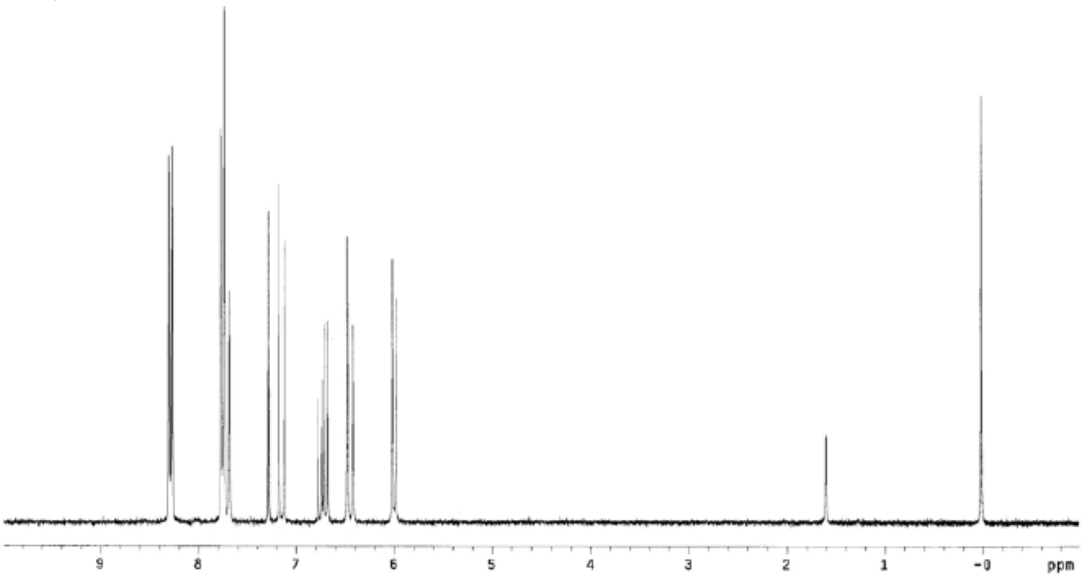


2.1b

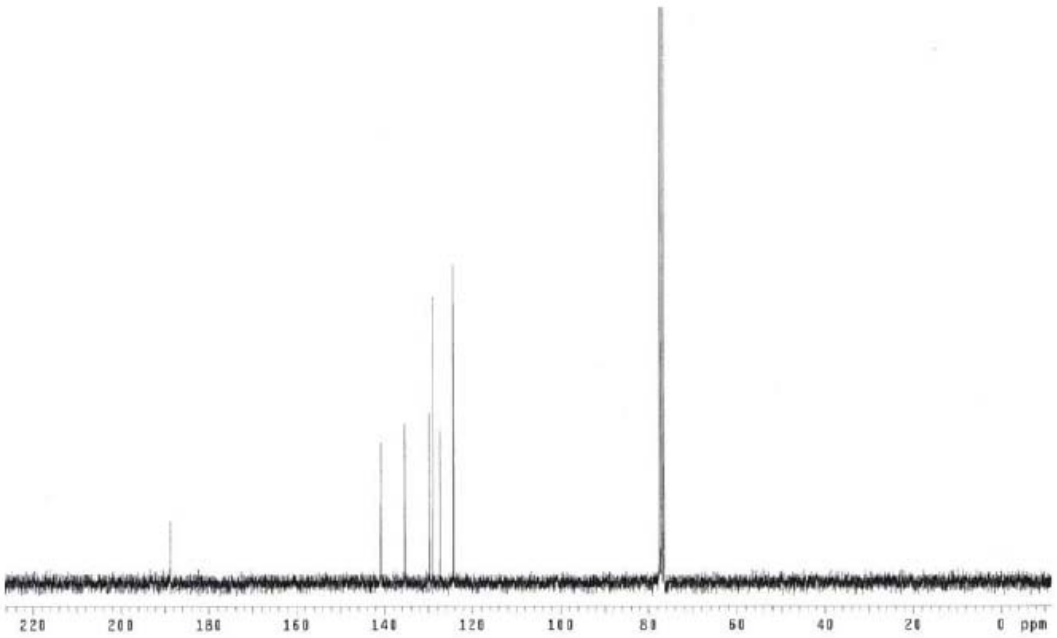
To a solution of 1-(4-nitro-phenyl)-penta-1,4-diene-3-ol (1.89 g, 9.21 mmol, 100 mol%) in CH_2Cl_2 (50 mL) at 0 ^oC was added MnO_2 (8.00 g, 92.1 mmol, 1000 mol%). The reaction mixture was allowed to stir for 12 hours at ambient temperature, at which point the reaction mixture was filtered through a pad of celite with the aid of Et_2O. The resulting solution was evaporated and the residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (590 mg, 2.90 mmol) as a yellow solid (32 % yield).

TLC: R_f 0.3 (EtOAc/hexane, 1/7). ^1H NMR (300 MHz, $CDCl_3$): δ 8.28-8.26 (m, 2H), 7.75-7.73 (m, 2H), 7.69 (d, *J* = 12.0 Hz, 1H), 7.13 (d, *J* = 12.0 Hz, 1H), 6.71 (dd, *J* = 12.9, 8.1 Hz, 1H), 6.43 (dd, *J* = 12.9, 0.9 Hz, 1H), 5.98 (dd, *J* = 8.1, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 140.8, 140.7, 135.4, 129.7, 128.9, 127.3, 124.2. HRMS Calcd. for $C_{12}H_{14}O_2$ (M+1): 204.0661, Found: 204. 0663. FTIR (NaCl film): 2360, 1655, 1592, 1517, 1405, 1345, 1202, 1106, 982, 846 cm^{-1}. M.P.: 123-125 ^oC.

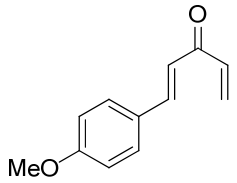
^{1}H NMR



^{13}C NMR



1-(4-Methoxy-phenyl)-penta-1,4-dien-3-one

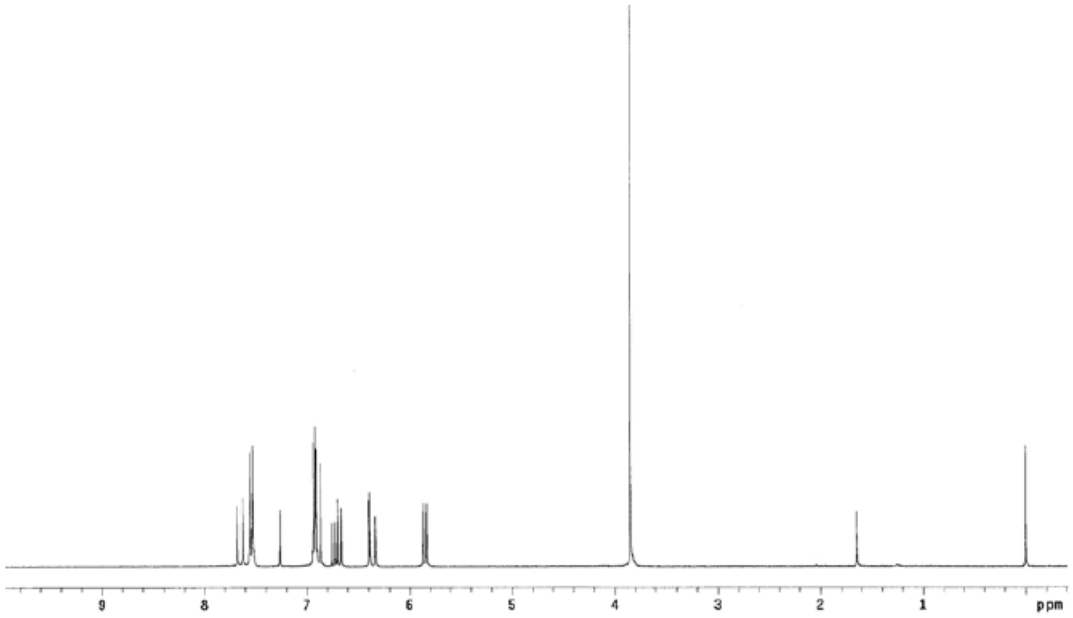


2.1d

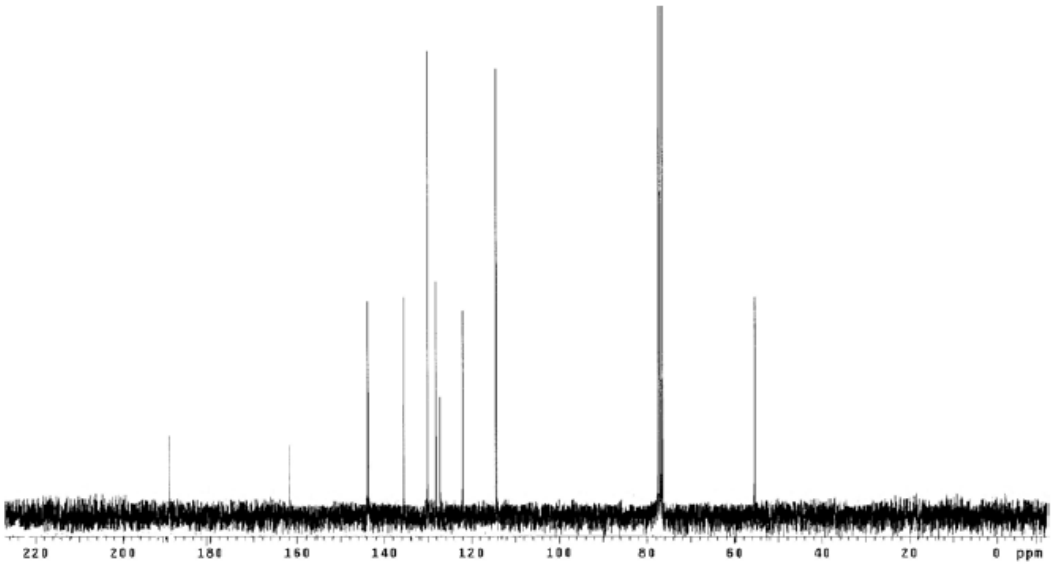
To a solution of 1-(4-methoxy-phenyl)-penta-1,4-dien-3-ol (2.32 g, 12.19 mmol, 100 mol%) in CH_2Cl_2 (50 mL) at 0 ^oC was added MnO_2 (10.60 g, 121.95 mmol, 1000 mol%). The reaction mixture was allowed to stir for 12 hours at ambient temperature, at which point the reaction mixture was filtered through a pad of celite with the aid of Et_2O. The resulting solution was evaporated and the residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (1.56 g, 8.29 mmol) as a yellow solid (68 % yield).

TLC: R_f 0.3 (EtOAc/hexane, 1/4). ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 15.9 Hz, 1H), 7.56-7.53 (m, 2H), 6.94-6.91 (m, 2H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.71 (dd, *J* = 17.4, 10.5 Hz, 1H), 6.36 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.85 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5, 161.7, 143.8, 135.5, 130.1, 128.1, 127.3, 122.0, 114.4, 55.4. HRMS Calcd. for $C_{12}H_{12}O_2$ (M+1): 189.0916, Found: 189.0912. FTIR (NaCl film): 2966, 1652, 1619, 1600, 1571, 1511, 1462, 1423, 1403, 1306, 1255, 1221, 1199, 1173, 1102, 1028, 987, 829 cm^{-1}. M.P.: 67-69 ^oC.

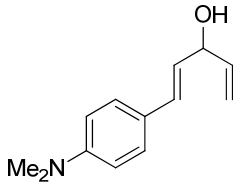
^{1}H NMR



^{13}C NMR



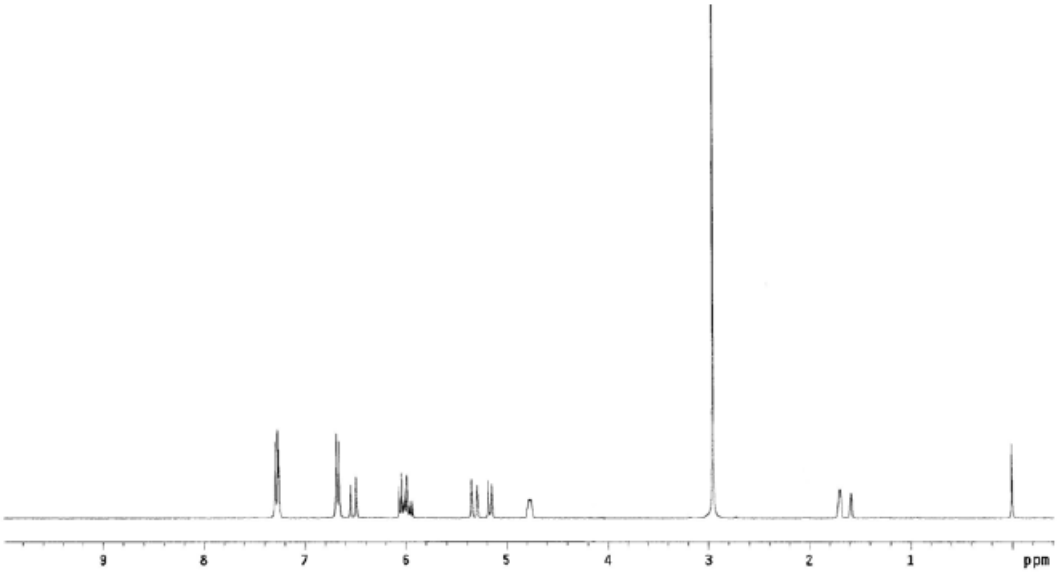
1-(4-Dimethylamino-phenyl)-penta-1,4-dien-3-ol



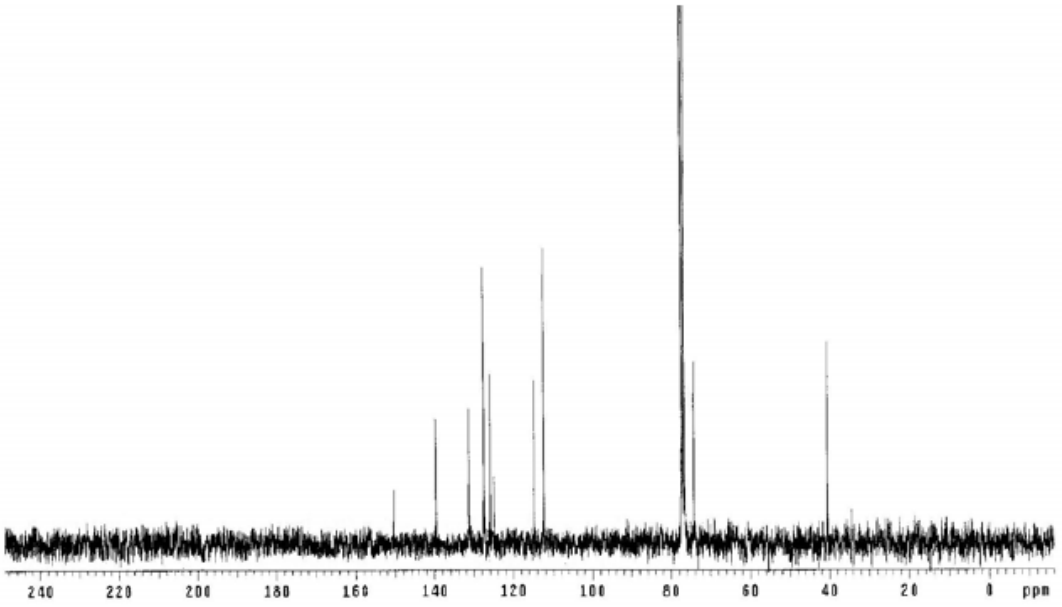
To a solution of vinylmagnesium bromide (1.0 M in THF, 37.1 mL, 37.1 mmol, 130 mol%) was added a solution of 3-(4-dimethylamino-phenyl)-propenal (5.0 g, 28.5 mmol, 100 mol%) in THF (25 mL) at -78 ^{o}C. The reaction mixture was allowed to stir for 2 hours at ambient temperature, at which point the reaction mixture was cooled to 0 ^{o}C and saturated NH_4Cl (aq.) was added. The reaction mixture was extracted with Et_2O (3 times). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (4.29 g, 21.1 mmol) as a viscous yellow oil (74 % yield).

TLC: R_f 0.3 (EtOAc/hexane, 1/4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2H), 6.68-6.66 (m, 2H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.03 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.99 (ddd, *J* = 17.4, 10.5, 5.7 Hz, 1H), 5.32 (d, *J* = 17.4 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H). 4.77 (dd, *J* = 7.2, 5.7 Hz, 1H), 2.96 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.2, 139.7, 131.3, 127.5, 125.9, 124.8, 114.9, 112.3, 74.3, 40.4. HRMS Calcd. for $C_{13}H_{17}NO$ (M): 203.1310, Found: 203.1312. FTIR (NaCl film): 3362, 2885, 2360, 1609, 1521, 1444, 1354, 1229, 1186, 1166, 965, 946, 805, 668 cm^{-1}.

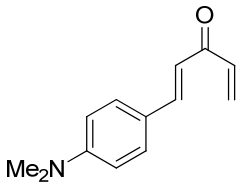
^{1}H NMR



^{13}C NMR



1-(4-Dimethylamino-phenyl)-penta-1,4-dien-3-one

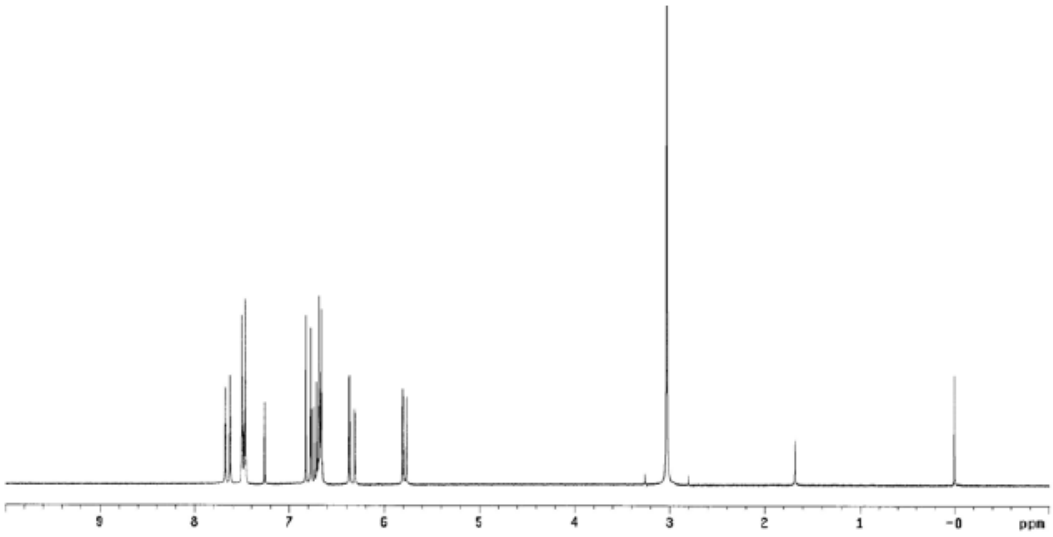


2.1e

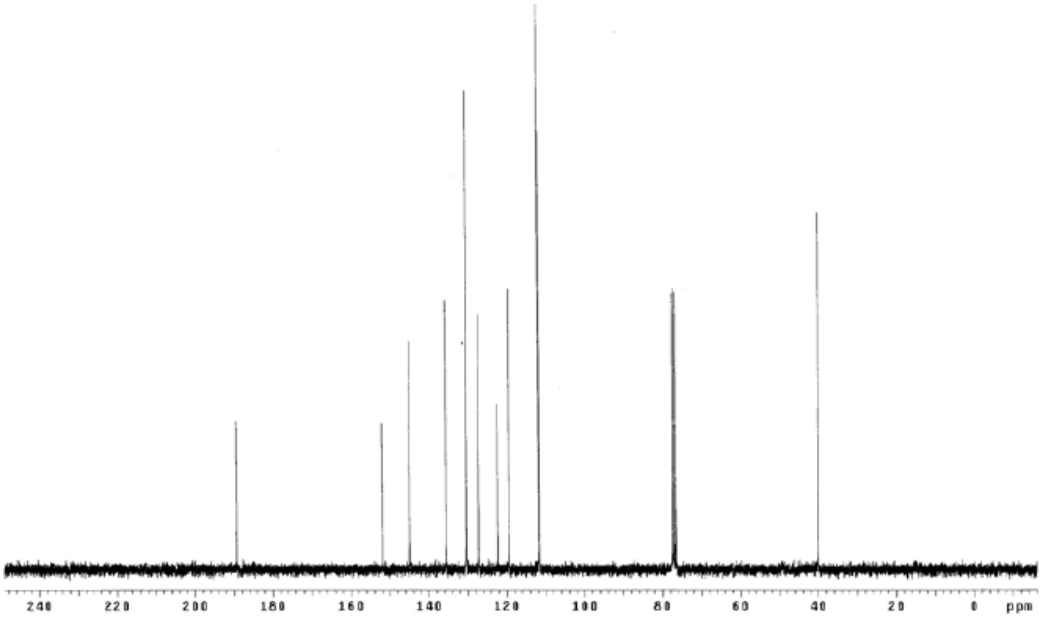
To a solution of 1-(4-dimethylamino-phenyl)-penta-1,4-dien-3-ol (2.12 g, 10.43 mmol, 100 mol%) in CH_2Cl_2 (50 mL) at 0 ^oC was added MnO_2 (9.06 g, 104.30 mmol, 1000 mol%). The reaction mixture was allowed to stir for 12 hours at ambient temperature, at which point the reaction mixture was filtered through a pad of celite with the aid of Et_2O. The resulting solution was evaporated and the residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (1.47 g, 7.30 mmol) as a red solid (70 % yield).

TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 15.9 Hz, 1H), 7.48-7.45 (m, 2H), 6.79 (d, J = 15.9 Hz, 1H), 6.68 (dd, J = 17.4, 10.5 Hz, 1H), 6.67-6.64 (m, 2H), 6.33 (dd, J = 17.4, 1.5 Hz, 1H), 5.77 (dd, J = 10.5, 1.5 Hz, 1H), 3.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.3, 152.0, 144.8, 135.6, 130.2, 127.1, 119.4, 111.7, 40.0. HRMS Calcd. for $C_{13}H_{15}NO$ (M+1): 202.1232, Found: 202.1231. FTIR (NaCl film): 2916, 1648, 1605, 1572, 1522, 1455, 1226, 985, 814 cm^{-1}. M.P.: 95-96 ^oC.

^{1}H NMR



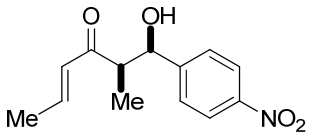
^{13}C NMR



Generarl Procedure for Reductive Aldol coupling of Divinyl ketones via Rhodium-Catalyzed Hydrogenation

To a 13 mm × 100 mm test-tube were added Li_2CO_3 (3.9 mg, 0.05 mmol, 10 mol%), $(2\text{-Fur})_3P$ (13.9 mg, 0.06 mmol, 12 mol%), $Rh(cod)_2SbF_6$ (13.9 mg, 0.025 mmol, 5 mol%), aldehyde (0.5 mmol, 100 mol%) and CH_2Cl_2 (0.5 mL, 1.0 M). The test-tube was sealed and the reaction system was purged with Ar(g) and H_2(g) for 20 seconds each. The reaction system was placed under one atmosphere of hydrogen using a balloon and divinyl ketone (1.0 mmol, 200 mol%) was added to the reaction mixture. The reaction mixture was allowed to stir at ambient temperature for 7 hours, at which point the reaction mixture was directly deposited onto a column of silica and purified chromatographically (SiO_2: EtOAc/hexane) to afford the title compound.

1-Hydroxy-2-methyl-1-(4-nitro-phenyl)-hex-4-en-3-one

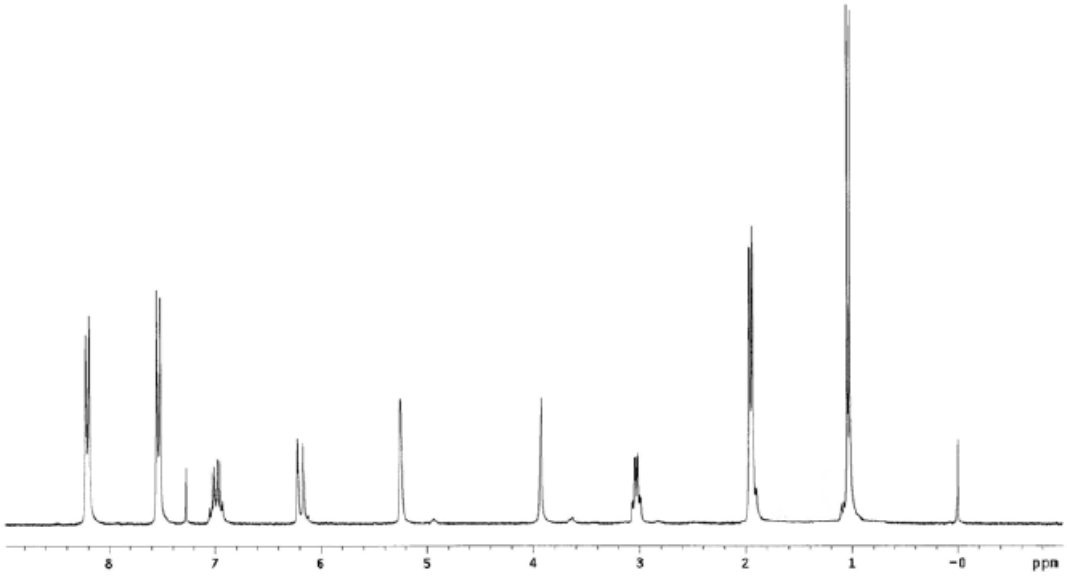


2.3a

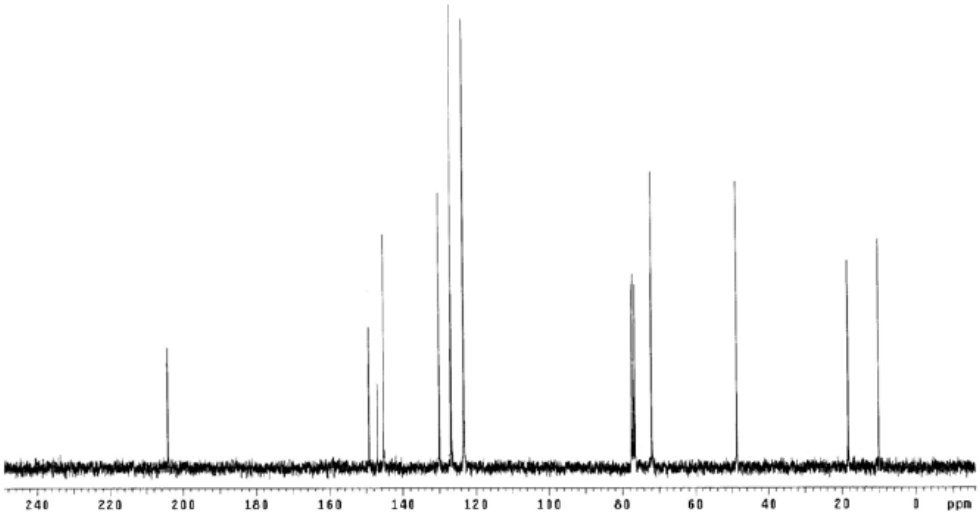
TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22-8.19 (m, 2H), 7.55-7.52 (m, 2H), 6.99 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.19 (dq, *J* = 15.6, 1.8 Hz, 1H), 5.24 (d, *J* = 2.7 Hz, 1H), 3.93 (br, 1H), 3.03 (dq, *J* = 7.2, 2.7 Hz, 1H), 1.95 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 149.3, 147.0, 145.3, 130.0, 126.7, 123.3, 71.9, 48.8, 18.3, 10.1. HRMS Calcd. for $C_{13}H_{15}NO_4$ (M):

250.1079; Found: 250.1082. FTIR (NaCl film): 3461, 2975, 2937, 2369, 1683, 1651, 1624, 1605, 1519, 1441, 1375, 1347, 1201, 1108, 1056, 970, 854, 749, 707, 668 cm^{-1}.

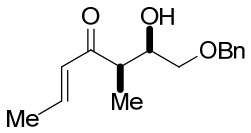
^{1}H NMR



^{13}C NMR



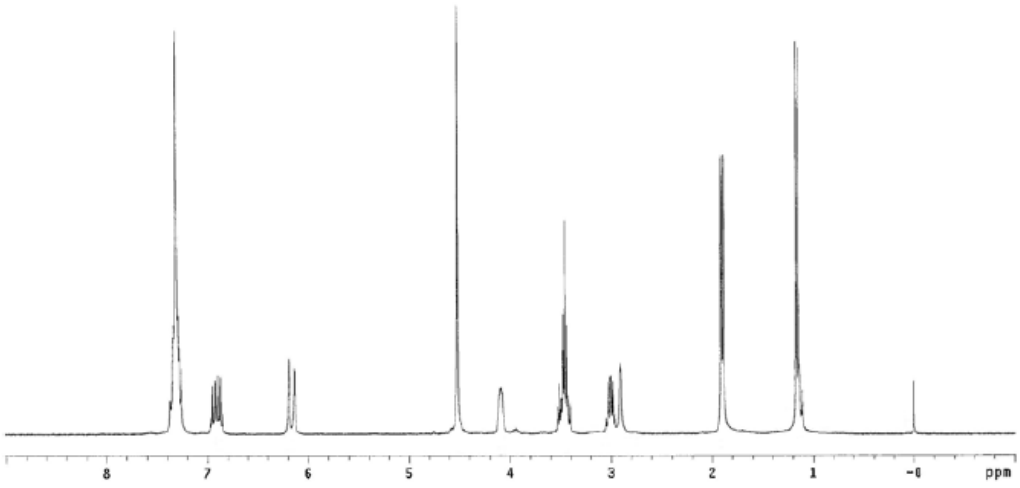
7-Benzyloxy-6-hydroxy-5-methyl-hept-2-en-4-one



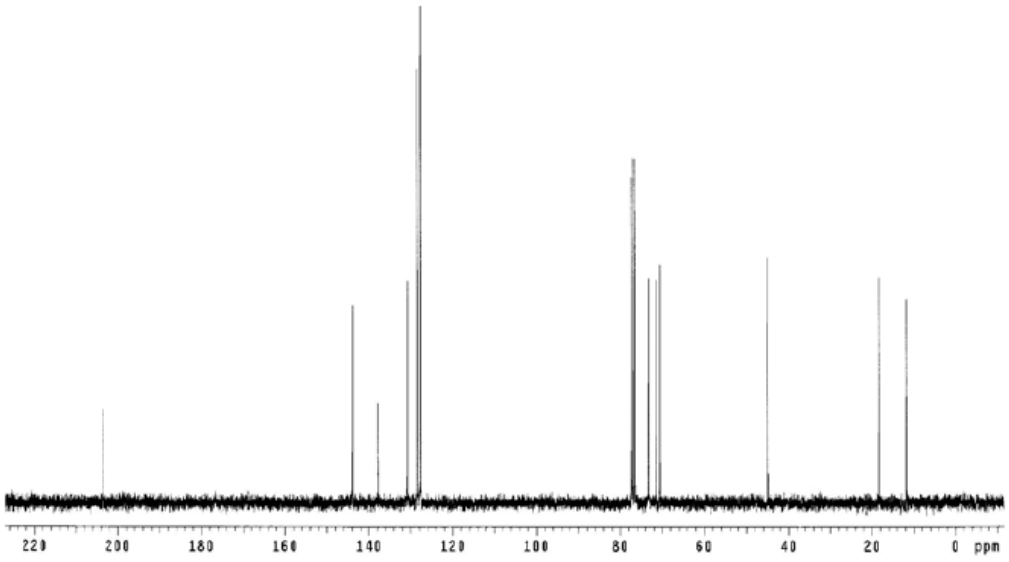
2.3b

TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 6.91 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.16 (dq, *J* = 15.6, 1.5 Hz, 1H), 4.52 (s, 2H), 4.04-4.14 (m, 1H), 3.53-3.41 (m, 2H), 3.01 (dq, *J* = 7.2, 5.4 Hz, 1H), 2.91 (d, *J* = 3.3Hz, 1H), 1.90 (dd, *J* = 6.9, 1.5 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 143.9, 137.8, 130.8, 128.4, 127.7, 73.3, 71.5, 70.6, 45.0, 18.3, 11.8. HRMS Calcd. for $C_{12}H_{20}O_3$ (M+1): 249.1491, Found: 249.1497. FTIR (NaCl film): 3447, 2912, 2360, 1654, 1626, 1453, 1374, 1101, 970, 738, 698, 668 cm^{-1}.

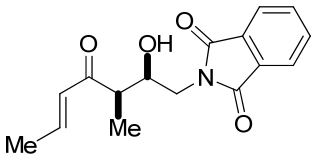
^{1}H NMR



^{13}C NMR



2-(2-Hydroxy-3-methyl-4-oxo-hept-5-enyl)-isoindole-1,3-dione

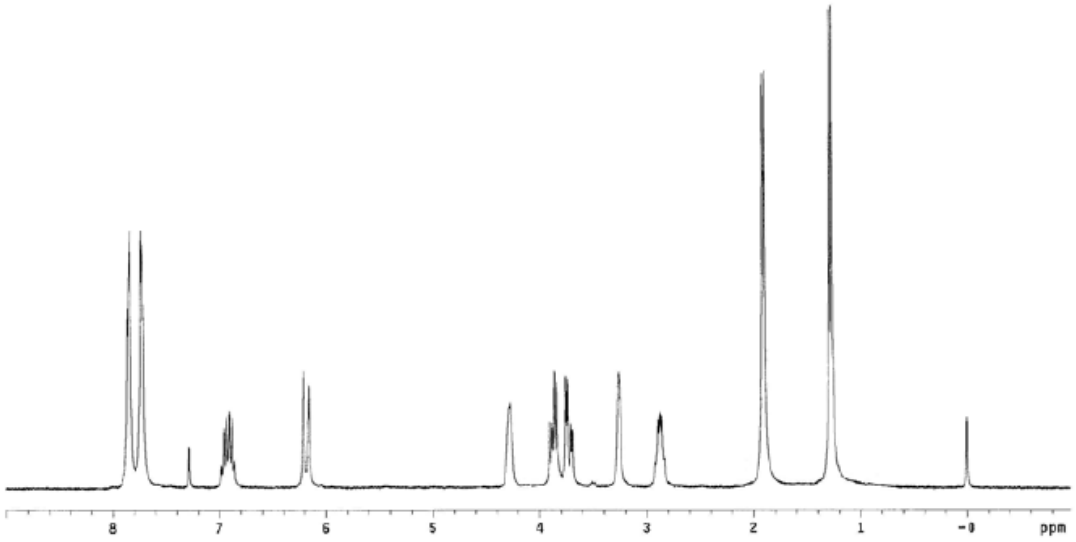


2.3c

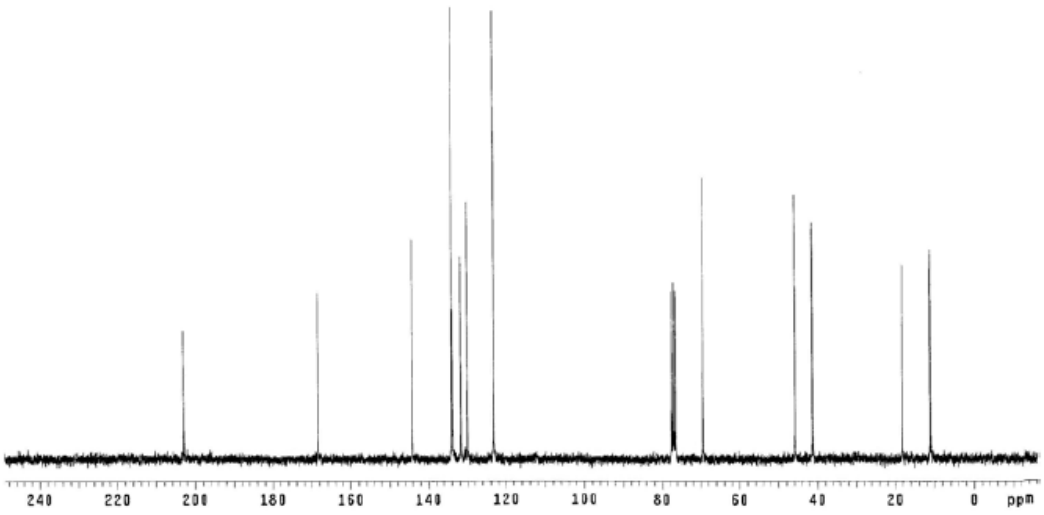
TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 7.74-7.33 (m, 2H), 6.92 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 4.32-4.22 (m, 1H), 3.87 (dd, *J* = 14.1, 4.5 Hz, 1H), 3.73 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.26 (br, 1H), 2.88 (m, 1H), 1.91 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 168.5, 144.3, 134.0, 131.9, 130.1, 123.3, 69.5, 45.8, 41.3, 18.3, 11.0. HRMS Calcd. for $C_{16}H_{17}NO_4$ (M+1): 288.1236, Found: 288.1234. FTIR (NaCl film):

3472, 2937, 2360, 1772, 1712, 1625, 1431, 1395, 1190, 1034, 969, 714 cm^{-1}. M.P.: 110-112 ^{o}C.

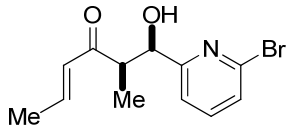
^{1}H NMR



^{13}C NMR



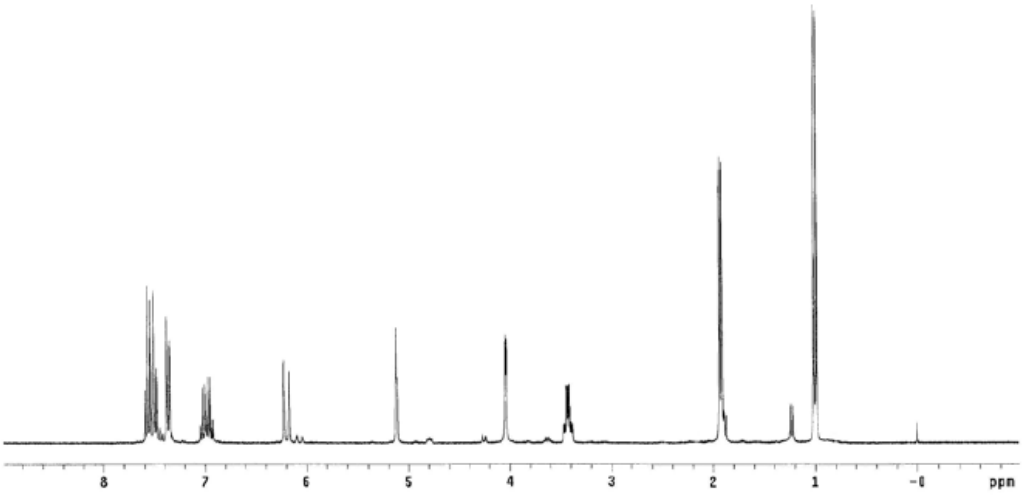
1-(6-Bromo-pyridin-2-yl)-1-hydroxy-2-methyl-hex-4-en-3-one



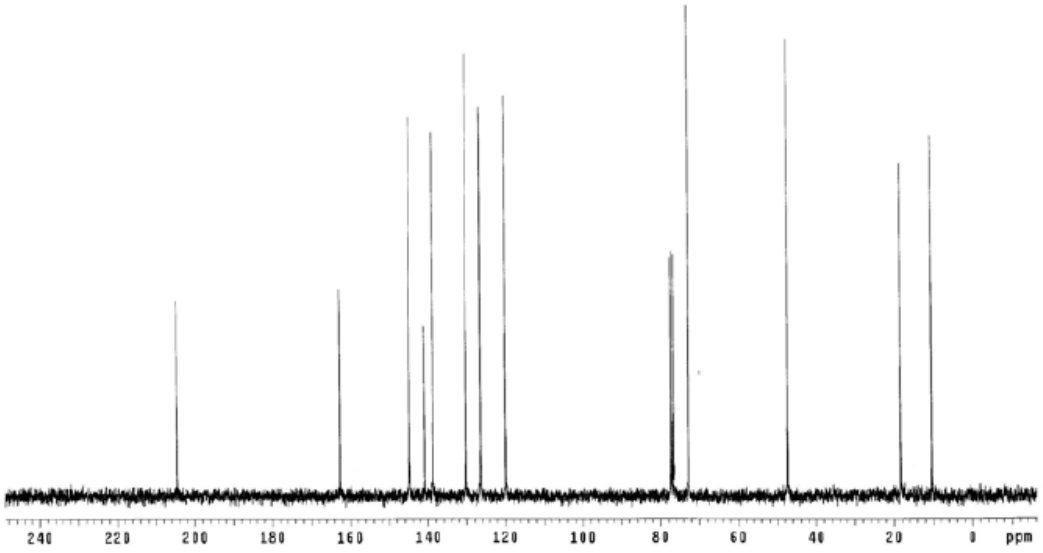
2.3d

TLC: R_f 0.5 (EtOAc/hexane, 1/2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.48 (m, 2H), 7.38-7.35 (m, 2H), 6.99 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.20 (dq, *J* = 15.6, 1.5 Hz, 1H), 5.12 (dd, *J* = 3.3, 3.3 Hz, 1H), 4.04 (d, *J* = 3.3 Hz, 1H), 3.43 (dq, *J* = 6.9, 3.3 Hz, 1H), 1.93 (dd, *J* = 6.9, 1.5 Hz, 3H), 1.93 (dd, *J* = 6.9, 1.5 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 162.5, 144.8, 140.9, 138.8, 130.1, 126.3, 119.9, 72.8, 47.3, 18.3, 10.3. HRMS Calcd. for $C_{12}H_{14}BrNO_2$ (M+1): 284.0286, Found: 284.0283. FTIR (NaCl film): 3443, 2973, 2935, 2360, 1684, 1653, 1626, 1582, 1555, 1437, 1406, 1375, 1290, 1199, 1157, 1127, 1044, 986, 969, 933, 788, 747, 697 cm^{-1}.

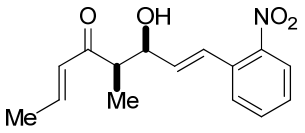
^{1}H NMR



^{13}C NMR



6-Hydroxy-5-methyl-8-(2-nitro-phenyl)-octa-2,7-dien-4- one

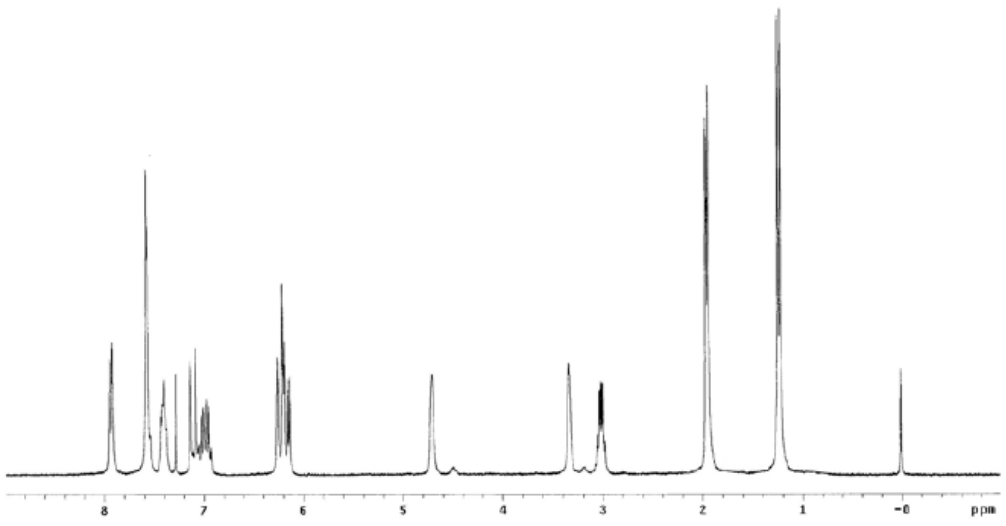


2.3e

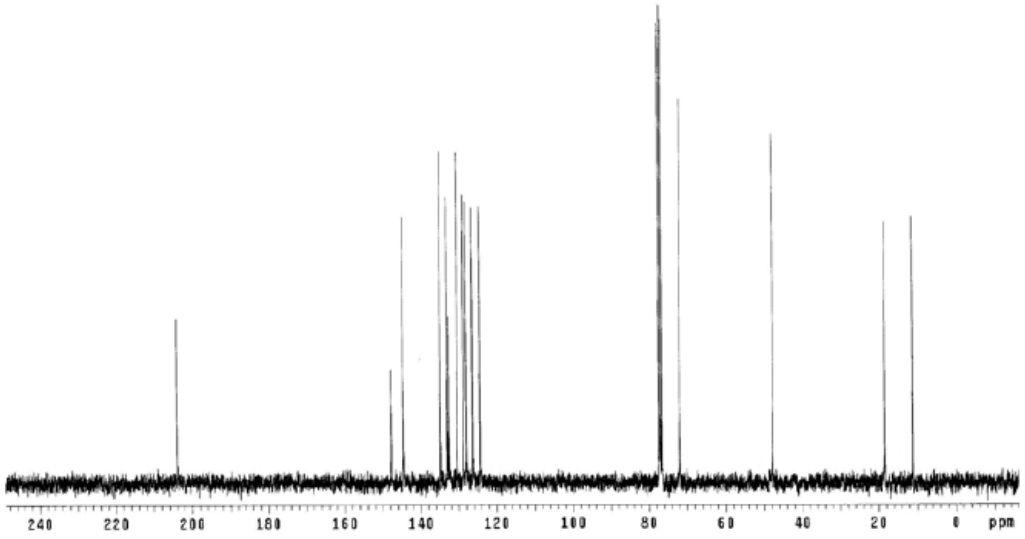
TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94-7.91 (m, 1H), 7.57-7.56 (m, 2H), 7.42-7.26 (m, 1H), 7.10 (d, *J* = 15.9 Hz, 1H), 6.98 (dq, *J* = 14.7, 6.9 Hz, 1H), 6.22 (d, *J* = 14.7 Hz, 1H), 6.16 (dd, *J* = 15.9, 5.7 Hz, 1H), 4.70 (dd, *J* = 5.7, 3.3 Hz, 1H), 3.24 (br, 1H), 3.01(dq, *J* = 7.5, 3.3 Hz, 1H), 1.95 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 147.7, 144.6, 134.8, 133.0, 132.6, 130.4, 128.8, 128.0, 126.3, 124.4, 71.8, 47.7, 18.3, 11.1. HRMS Calcd. for $C_{15}H_{17}NO_4$ (M+1): 276.1236, Found: 276.1238. FTIR (NaCl film): 3447, 2973, 2933, 2359, 2341,

1685, 1654, 1624, 1570, 1522, 1441, 1345, 1302, 1199, 1042, 967, 860, 785, 742, 668 cm^{-1}.

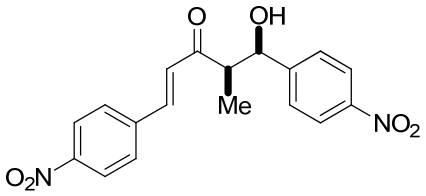
^{1}H NMR



^{13}C NMR



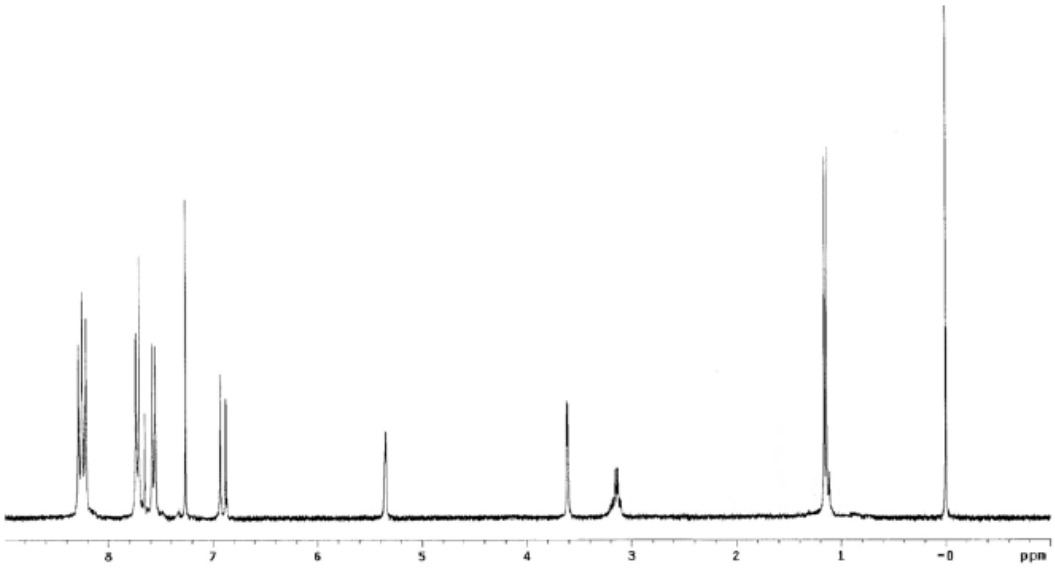
5-Hydroxy-4-methyl-1,5-bis-(4-nitro-phenyl)-pent-1-en-3-one



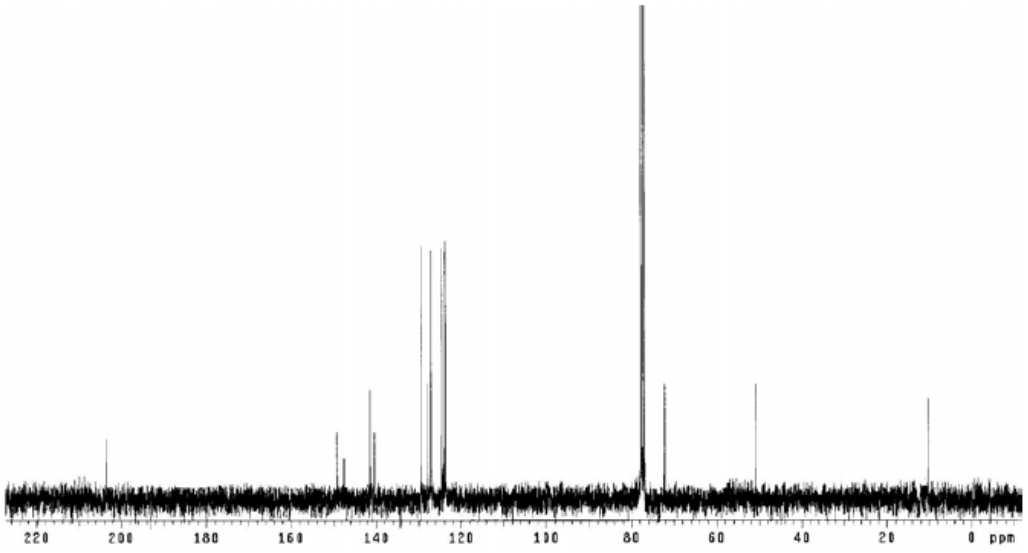
2.4b

TLC: R_f 0.3 (EtOAc/hexane, 1/2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29-8.26 (m, 5H), 7.74-7.71 (m, 2H), 7.59-7.56 (m, 2H), 6.91 (d, *J* = 15.9 Hz, 1H), 3.61 (d, *J* = 2.4 Hz, 1H), 3.14 (dq, *J* = 7.5, 2.7 Hz, 1H), 1.15 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 149.2, 149.1, 147.5, 141.5, 140.4, 129.4, 127.7, 127.1, 124.5, 124.0, 123.8, 72.2, 51.0, 10.3. HRMS Calcd. for $C_{18}H_{16}NO_6$ (M+1): 357.1087, Found: 357.1083. FTIR (NaCl film): 3495, 3107, 2360, 1684, 1596, 1516, 1344, 1108, 848 cm^{-1}. M.P.: 140-142 ^oC.

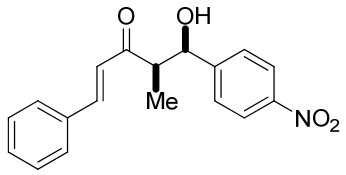
^{1}H NMR



^{13}C NMR



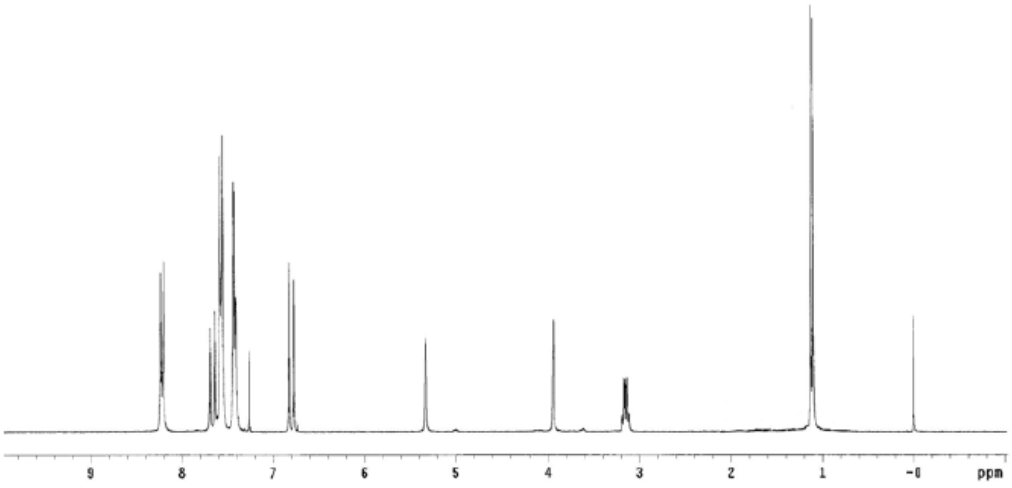
5-Hydroxy-4-methyl-5-(4-nitro-phenyl)-1-phenyl-pent-1-en-3- one



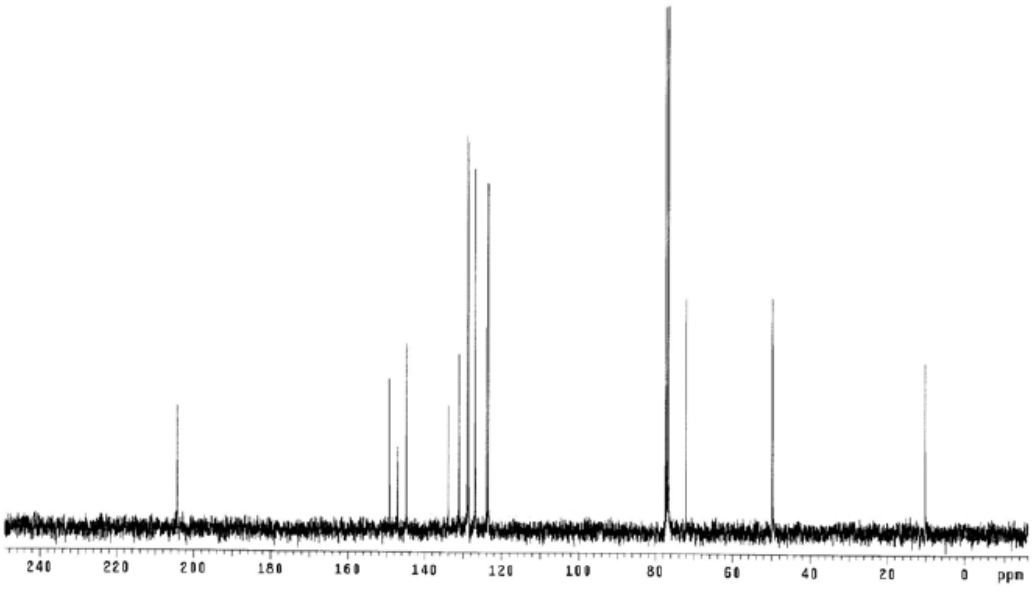
2.4c

TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24-8.21 (m, 2H), 7.67 (d, *J* = 15.9 Hz, 1H), 7.59-7.56 (m, 4H), 7.45-7.41 (m, 3H), 6.80 (d, *J* = 15.9 Hz, 1H), 5.36-5.30 (m, 1H), 3.94 (br, 1H), 3.15 (dq, *J* = 7.5, 2.7 Hz, 1H), 1.12 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 149.2, 144.6, 133.9, 131.1, 129.0, 128.5, 126.8, 124.0, 123.4, 72.0, 49.8, 10.1. HRMS Calcd. for $C_{18}H_{17}NO_4$ (M+1): 312.1236, Found: 312.1241. FTIR (NaCl film): 3445, 2941, 1678, 1603, 1575, 1517, 1449, 1345, 1184, 1107, 1051, 982, 852, 764, 707 cm^{-1}.

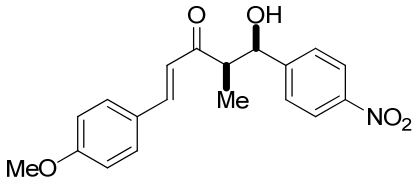
^{1}H NMR



^{13}C NMR



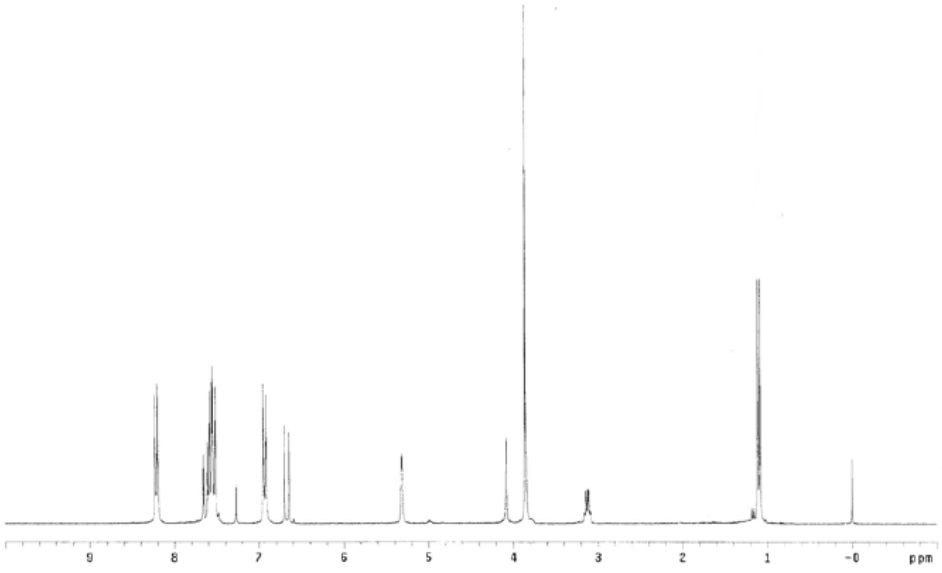
5-Hydroxy-1-(4-methoxy-phenyl)-4-methyl-5-(4-nitro-phenyl)-pent-1-en-3-one



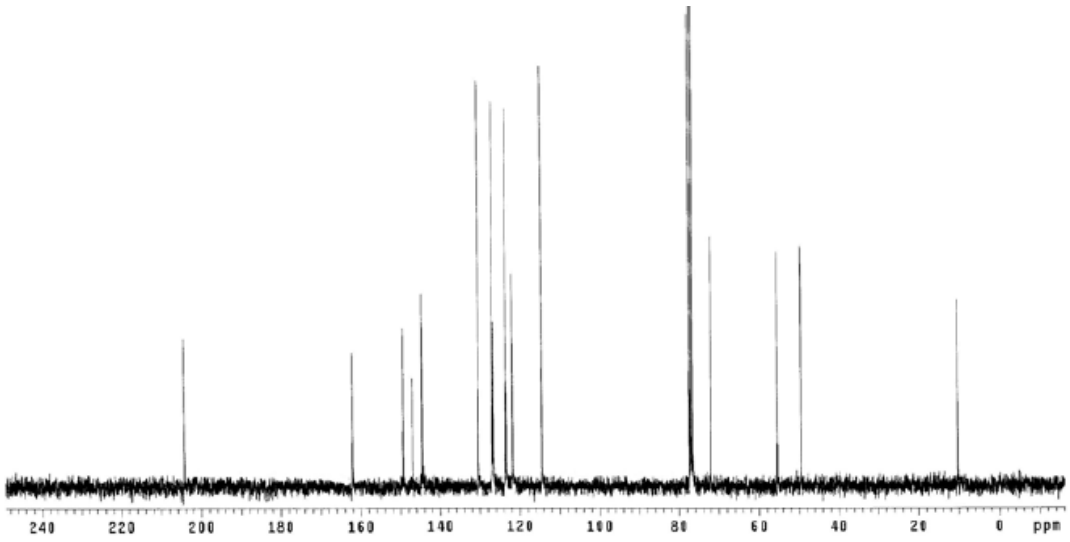
2.4d

TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23-8.20 (m, 2H), 7.63 (d, *J* = 15.9 Hz, 1H), 7.59-7.52 (m, 4H), 6.95-6.92 (m, 2H), 6.67 (d, *J* = 15.9 Hz, 1H), 5.34-5.30 (m, 1H), 4.08 (br, 1H), 3.86 (s, 3H), 3.12 (dq, *J* = 7.5, 2.7 Hz, 1H), 1.10 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 162.1, 149.3, 147.0, 144.5, 130.4, 126.8, 126.5, 123.4, 121.7, 114.5, 72.1, 55.4, 49.5, 10.2. HRMS Calcd. for $C_{19}H_{19}NO_5$ (M+1): 342.1341, Found: 342.1344. FTIR (NaCl film): 3448, 2935, 1596, 1571, 1511, 1458, 1422, 1345, 1255, 1172, 1108, 1028, 984, 853, 828, 705 cm^{-1}. M.P.: 98-90 ^oC.

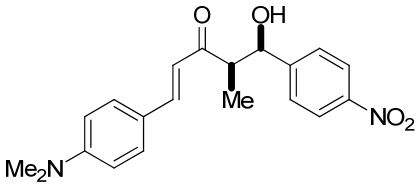
^{1}H NMR



^{13}C NMR



1-(4-Dimethylamino-phenyl)-5-hydroxy-4-methyl-5-(4-nitro-phenyl)-pent-1-en-3-one

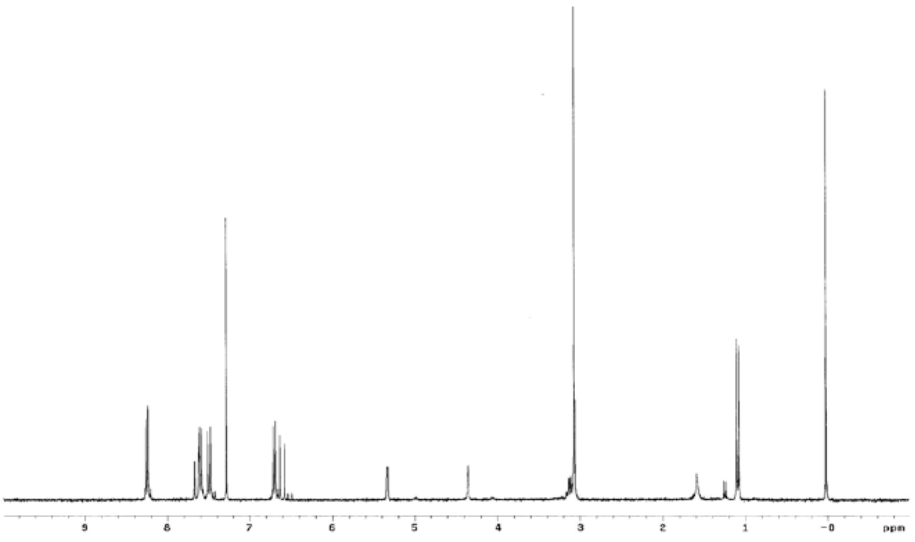


2.4e, 2.5a

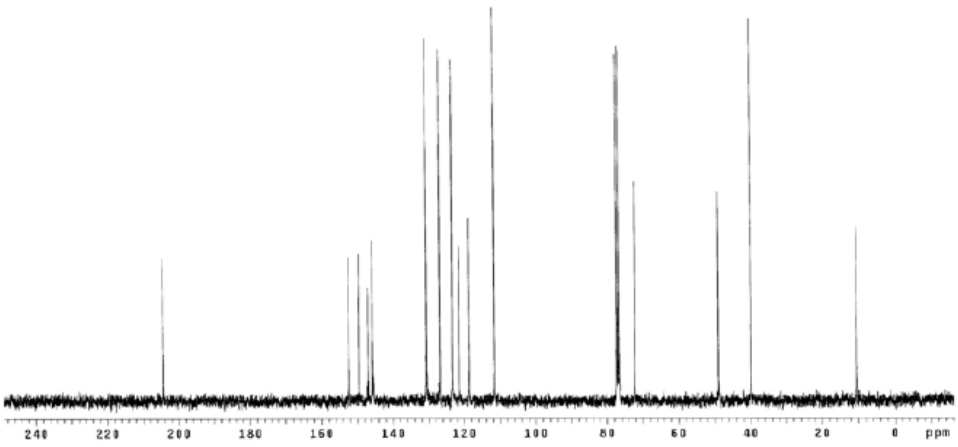
TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24-8.21 (m, 2H), 7.63 (d, *J* = 15.9 Hz, 1H), 7.59-7.56 (m, 2H), 7.49-7.46 (m, 2H), 6.58 (d, *J* = 15.9 Hz, 1H), 5.24-5.26 (m, 1H), 4.34 (br, 1H), 3.12 (dd, *J* = 7.5, 2.7 Hz 1H), 3.06 (s, 6H), 1.08 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 152.3, 149.5, 146.6, 130.6, 126.8, 123.3, 121.3, 118.6, 111.7, 72.2, 48.9, 39.9, 10.4. HRMS Calcd. for $C_{20}H_{22}N_2O_4$ (M):

354.1580, Found: 354.1581. FTIR (NaCl film): 3421, 2916, 1574, 1523, 1434, 1369, 1344, 1182, 1052, 853, 815 cm^{-1}. M.P.: 114-116 ^{o}C.

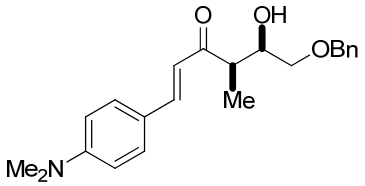
^{1}H NMR



^{13}C NMR



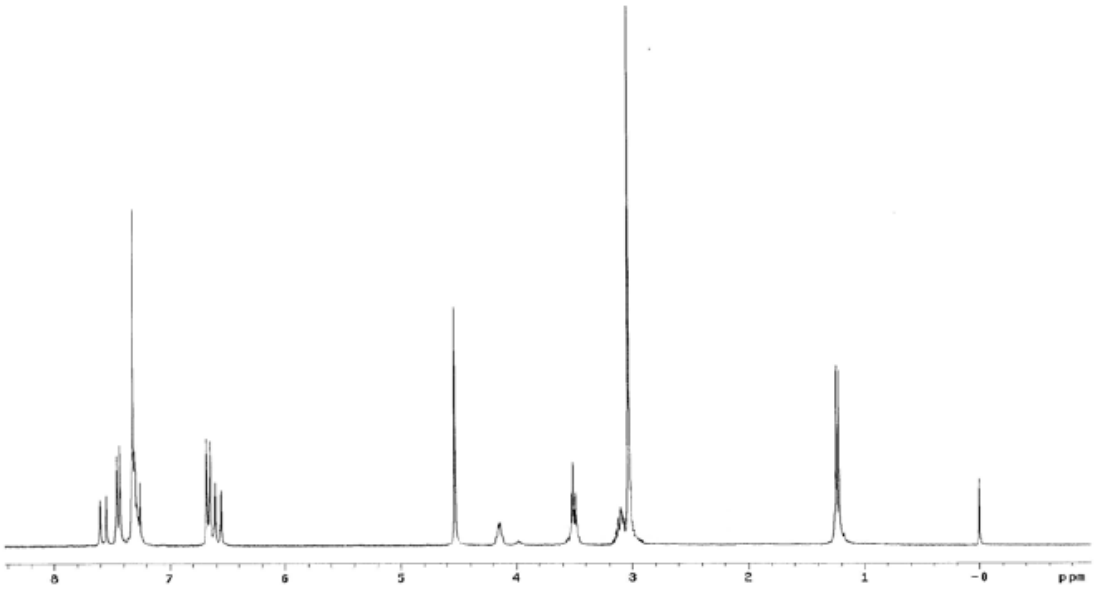
6-Benzyloxy-1-(4-dimethylamino-phenyl)-5-hydroxy-4-methyl-hex-1-en-3-one



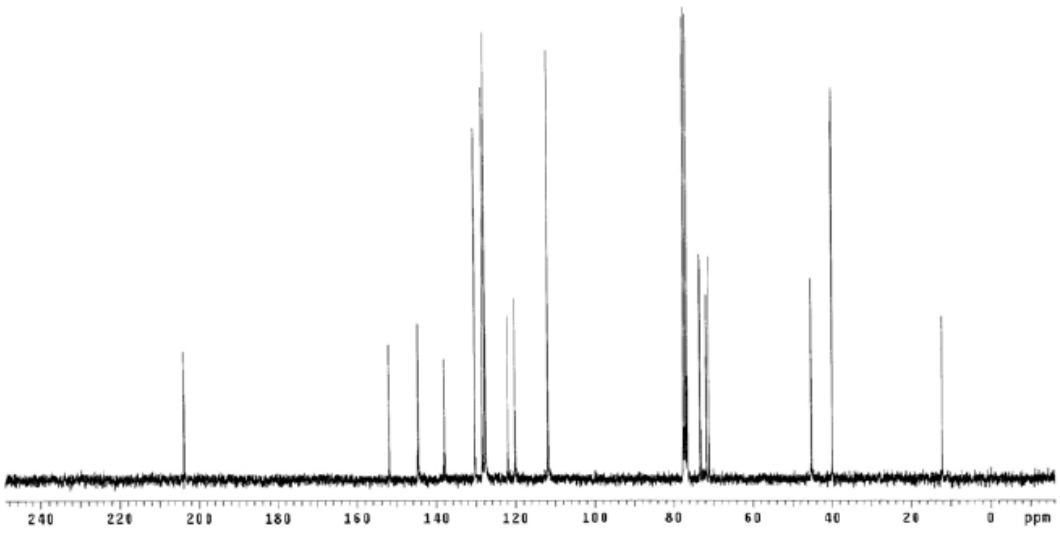
2.5b

TLC: R_f0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 15.9 Hz, 1H), 7.46-7.43 (m, 2H), 7.33-7.26 (m, 5H), 6.68-6.65 (m, 2H), 6.58 (d, *J* = 15.9 Hz, 1H), 4.53 (s, 2H), 4.19-4.10 (m, 1H), 3.58-3.46 (m, 2H), 3.14-2.98 (m, 8H), 1.23 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 152.0, 144.5, 137.9, 130.3, 128.3, 127.7, 127.6, 121.8, 120.0, 111.7, 73.3, 71.7, 70.9, 45.3, 40.0, 12.2. HRMS Calcd. for $C_{22}H_{27}NO_3$ (M+1): 354.2069, Found: 354.2067. FTIR (NaCl film): 3454, 2921, 1579, 1525, 1433, 1365, 1227, 1182, 1063, 984, 945, 815, 737, 698 cm^{-1}.

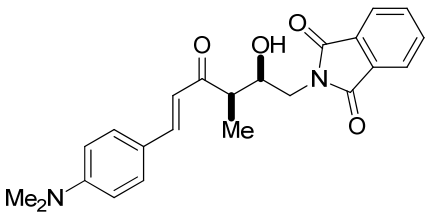
^{1}H NMR



^{13}C NMR



2-[6-(4-Dimethylamino-phenyl)-2-hydroxy-3-methyl-4-oxo-hex-5-enyl]-isoindole-1,3-dione

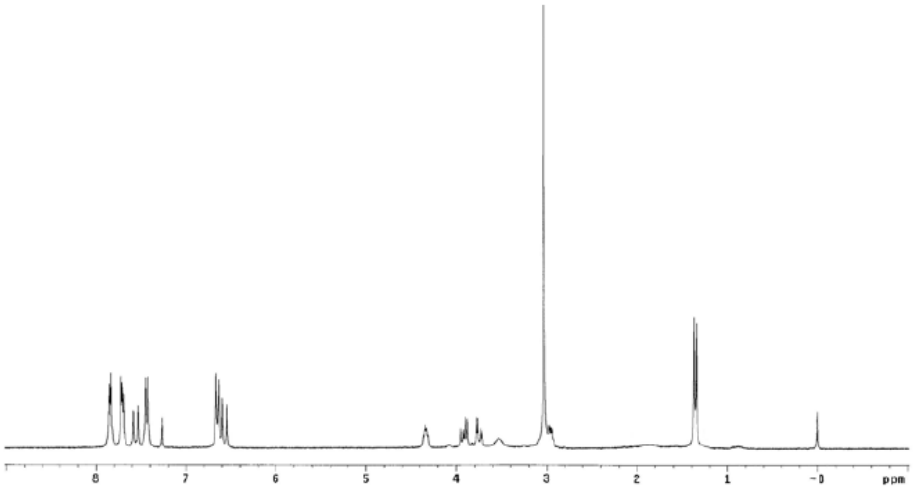


2.5c

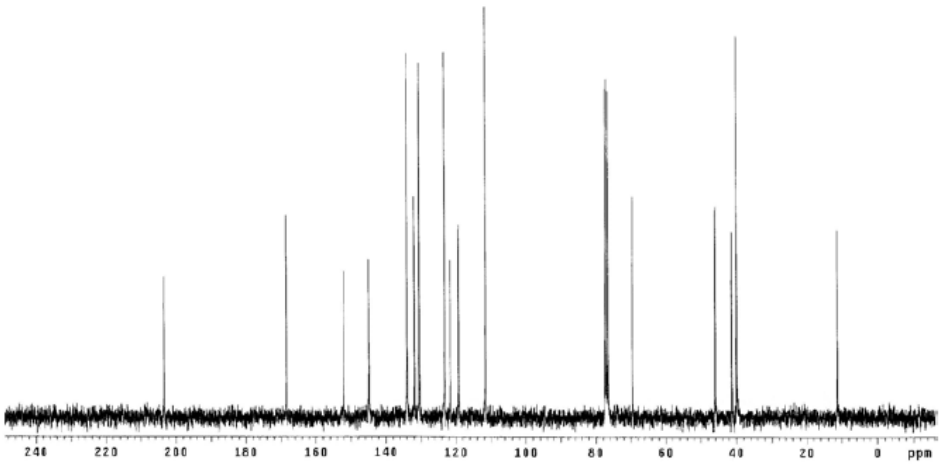
TLC: R_f 0.5 (EtOAc/hexane, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.83 (m, 2H), 7.72-7.69 (m, 2H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.45-7.42 (m, 2H), 6.69-6.64 (m, 2H), 6.58 (d, *J* = 15.6 Hz, 1H), 4.36-4.31 (m, 1H), 3.91 (dd, *J* = 14.1, 8.1 Hz, 1H), 3.55 (dd, *J* = 14.1, 4.5 Hz, 1H), 3.53(br, 1H), 3.03 (s, 6H), 3.03-2.90 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 168.4, 152.0, 144.8, 133.9, 131.8, 130.3, 123.2, 121.6, 119.1, 111.6, 69.5, 46.0, 41.3, 39.9, 11.2. HRMS Calcd. for $C_{23}H_{24}N_2O_4$ (M+1):

393.1814, Found: 393.1810. FTIR (NaCl film): 3463, 2922, 2368, 1710, 1577, 1524, 1432, 1394, 1366, 1183, 1033, 816, 714 cm^{-1}. M.P.: 154-156 ^{o}C.

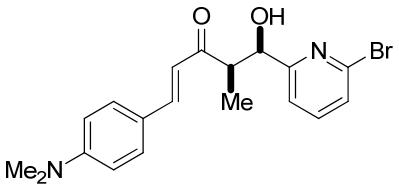
^{1}H NMR



^{13}C NMR



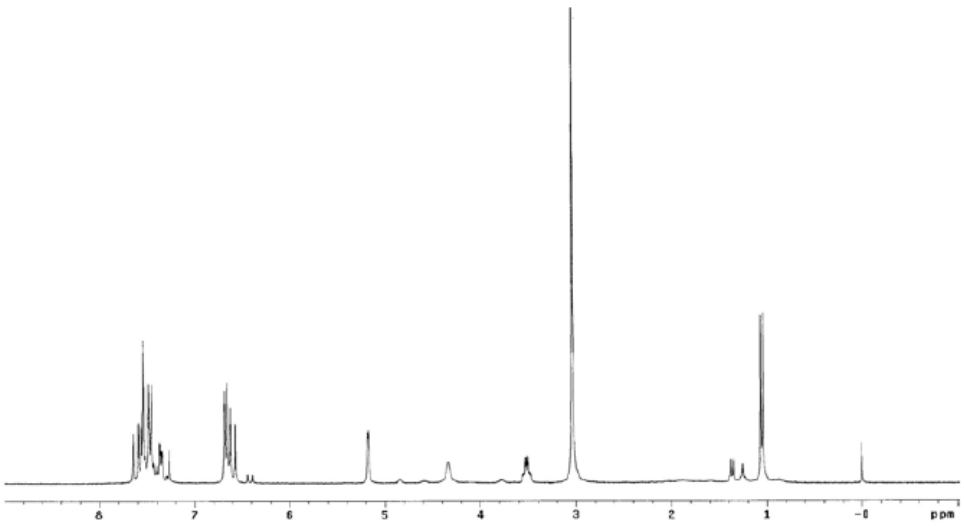
5-(6-Bromo-pyridin-2-yl)-1-(4-dimethylamino-phenyl)-5-hydroxy-4-methyl-pent-1-en-3-one



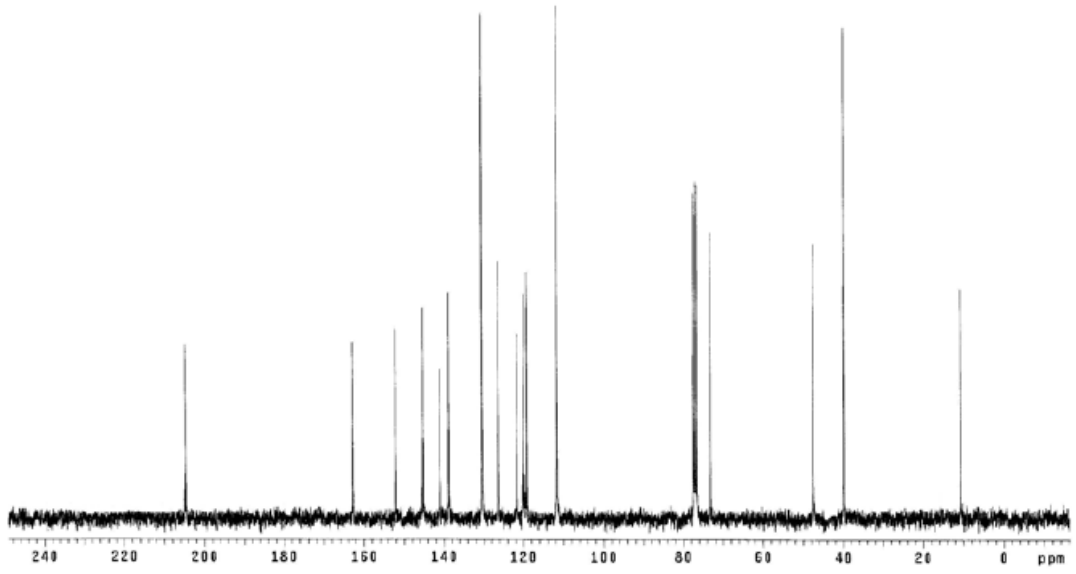
2.5d

TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 15.9 Hz, 1H), 7.56-7.34 (m, 5H), 6.69-6.66 (m, 2H), 6.60 (d, *J* = 15.9 Hz, 1H), 5.19 (d, *J* = 3.0 Hz, 1H), 4.33 (br, 1H), 3.52 (dq, *J* = 7.2, 3.0 Hz, 1H), 3.04 (s, 6H), 1.05 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 162.8, 152.1, 145.2, 140.9, 138.7, 130.4, 126.2, 121.6, 119.2, 111.6, 73.2, 47.5, 39.9, 10.7. HRMS Calcd. for $C_{19}H_{21}BrN_2O_2$ (M+1): 389.0865, Found: 389.0865. FTIR (NaCl film): 3425, 2917, 2360, 1597, 1524, 1434, 1366, 1182, 1052, 985, 945, 813 cm^{-1}. M.P.: 125-127 ^{o}C.

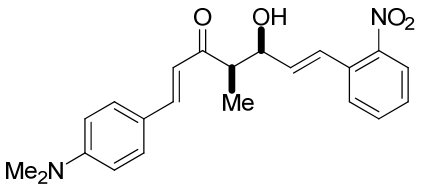
^{1}H NMR



^{13}C NMR



1-(4-Dimethylamino-phenyl)-5-hydroxy-4-methyl-7-(2-nitro-phenyl)-hepta-1,6-dien-3-one

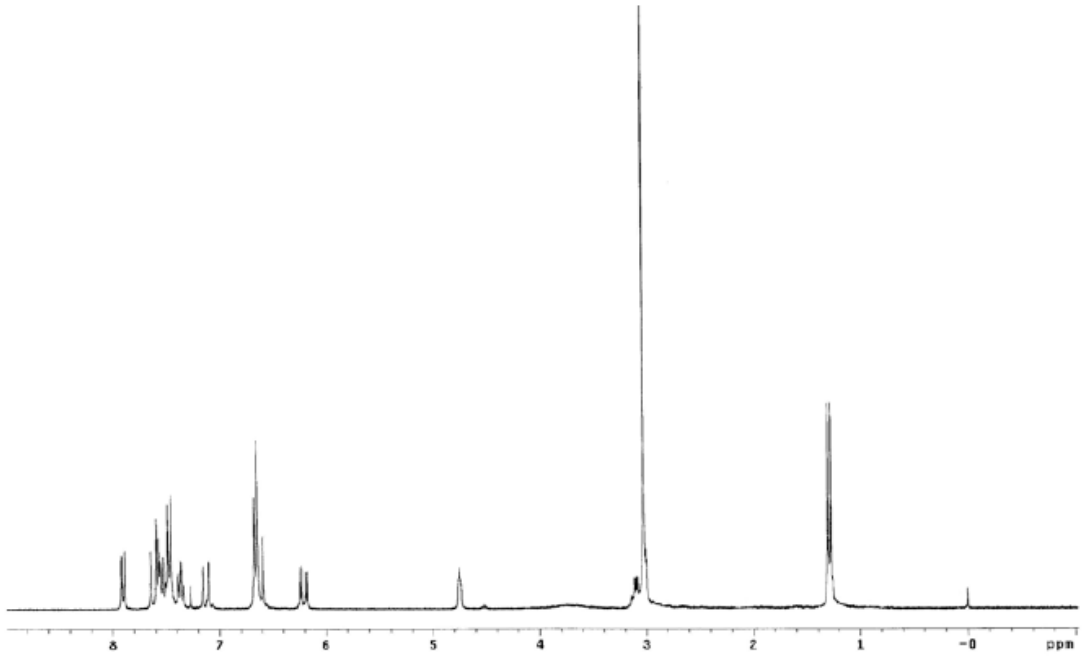


2.5e

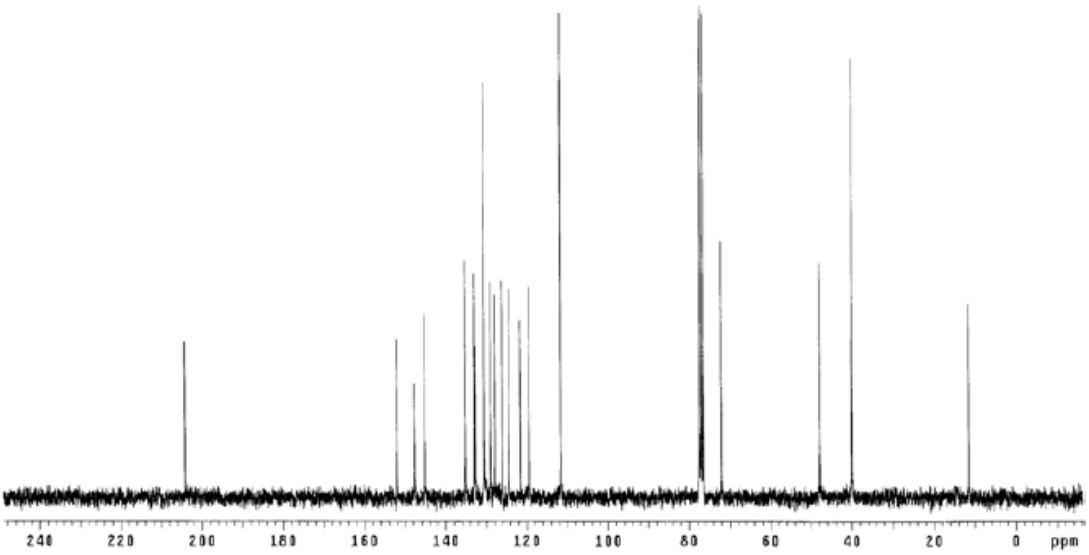
TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.89 (m, 1H), 7.62 (d, *J* = 15.6 Hz, 1H), 7.59-7.33 (m, 6H), 7.13 (d, *J* = 15.9 Hz, 1H), 6.68-6.64 (m, 2H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.21(dd, *J* = 15.9, 5.7 Hz, 1H), 4.75 (dd, *J* = 5.7, 3.3 Hz, 1H), 3.10 (dq, *J* = 15.6, 3.3 Hz, 1H), 3.03 (s, 6H), 3.03-3.00 (br, 1H), 1.29 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 152.1, 147.7, 145.1, 135.1, 133.0, 132.7, 130.5, 128.8, 127.9, 126.1, 124.3, 121.6, 119.3, 111.7, 72.1, 47.9, 40.0, 11.4. HRMS Calcd. for

$C_{22}H_{24}N_2O_4$ (M+1): 381.1814 ; Found: 381.1812 FTIR (NaCl film): 3424, 2926, 2359, 1577, 1523, 1434, 1344, 1182, 1168, 1053, 970, 946, 860, 815, 742 cm^{-1}.

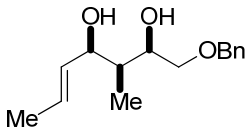
^1H NMR



^{13}C NMR



1-Benzyloxy-3-methyl-hept-5-ene-2,4-diol

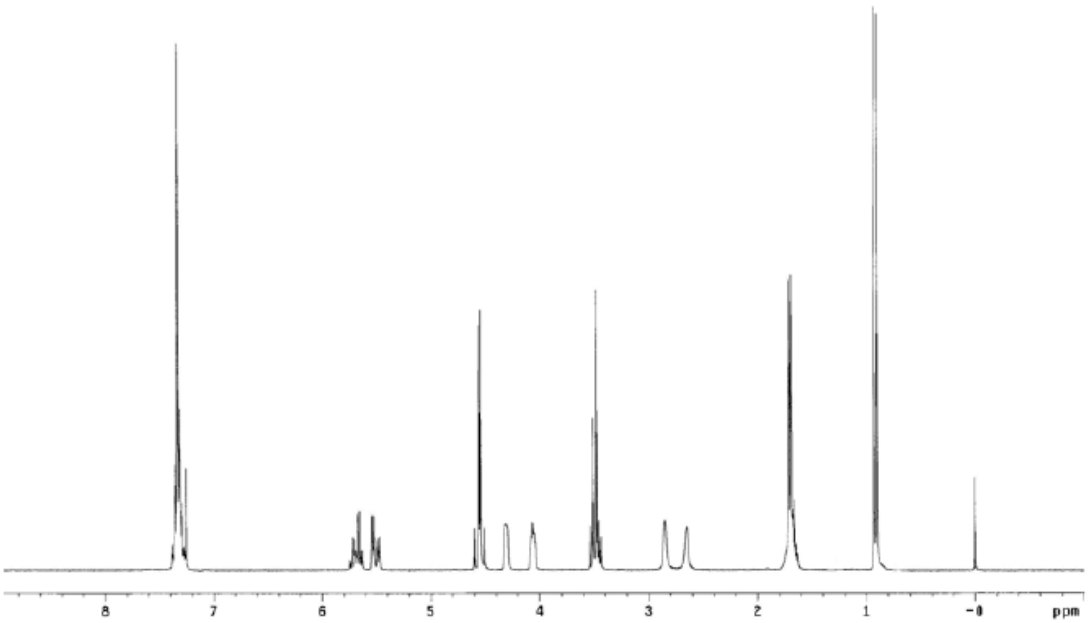


2.6a

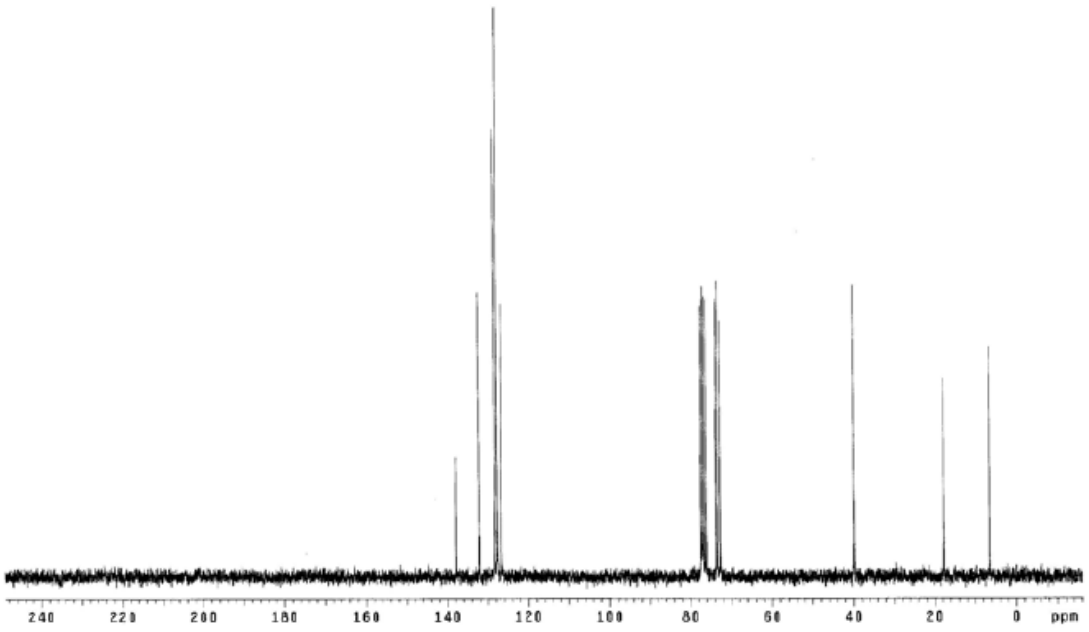
A solution of Et_3B (1.0M in hexane, 0.46 mL, 0.46 mmol, 119 mol%) was added to a mixture of dry THF (1.5 mL) and MeOH (0.6 mL) at ambient temperature under nitrogen. After 1hour, the mixture was cooled to -78 ^oC followed by the enone **2.3b** (96 mg, 0.39 mmol, 100 mol%) in THF (0.5 mL). The resulting solution was stirred for 1hour. Then $NaBH_4$ (18 mg, 0.46 mmol, 120 mol%) was added, and the mixture was stirred for 5 hours. The reaction mixture was diluted with ether (15 mL), and treated with saturated NH_4Cl (aq.) (15 mL). The layers were separated and the aqueous layer was extracted with ether (3x25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was azeotroped a few times with MeOH until boroncontaining compounds were removed. Flash chromatography (SiO_2: EtOAc/hexane) afforded the title compound (96 mg, 0.38 mmol) as colorless oil (98 % yield).

TLC: R_f 0.4 (EtOAc/hexane, 1/2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.74 (ddq, *J* = 15.3, 6.3, 1.2 Hz, 1H), 5.51 (ddq, *J* = 15.3, 6.0, 1.5 Hz, 1H), 4.55 (d, *J* = 1.2, 2H), 4.34-4.26 (m, 1H), 4.10-4.02 (m, 1H), 3.54-3.44 (m, 2H), 2.85 (br, 1H), 2.62 (br, 1H) 1.70 (dd, *J* = 6.3, 1.5 Hz, 3H), 1.69-1.63 (m, 1H), 0.92 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 132.2, 128.4, 127.7, 126.6, 76.1, 73.7, 73.4, 72.7, 39.9, 17.7, 6.4. HRMS Calcd. for $C_{15}H_{22}O_3$ (M+1): 251.1647, Found: 251.1648. FTIR (NaCl film): 3395, 3029, 2968, 2914, 2858, 1670, 1496, 1453, 1377, 1253, 1094, 966, 736, 698 cm^{-1}.

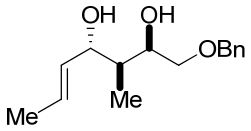
^{1}H NMR



^{13}C NMR



1-Benzyloxy-3-methyl-hept-5-ene-2,4-diol

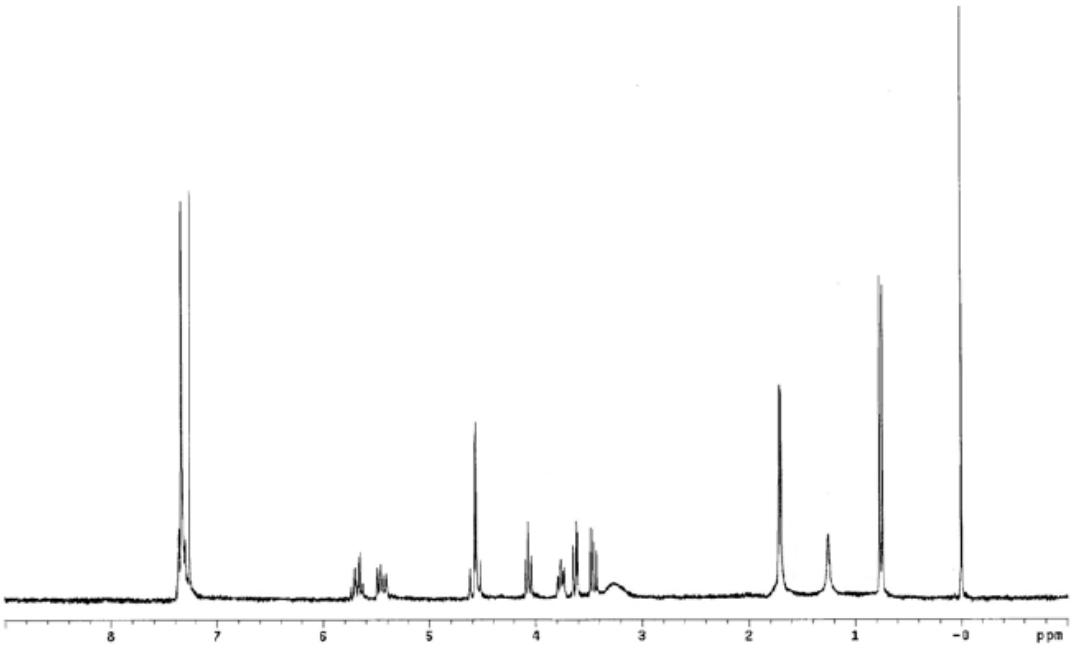


2.6b

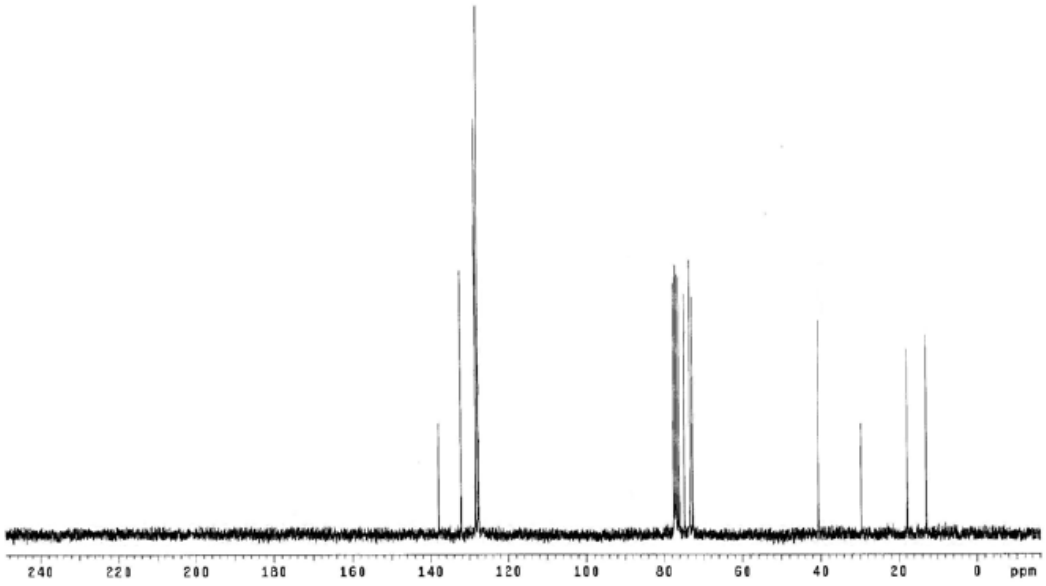
A solution of $Me_4NBH(OAc)_3$ (530 mg, 2.02 mmol, 1010 mol%) in AcOH (2.5 mL) and MeCN (2.5 mL) was prepared under Ar and stirred at ambient temperature for 20 min.The mixture was cooled to -30 ^oC. A solution of the enone **2.3b** (50 mg, 0.20 mmol, 100 mol%) in MeCN (2.5 mL) at 0 ^oC was added dropwise via cannular over 10 min. The resulting mixture was allowed to warm to -20 ^oC and stirred for 24 hours. CH_2Cl_2 was added to the reaction mixture, and then a saturated aqueous $NaHCO_3$ solution was slowly added. After 45 min at ambient temperature, the aqueous phase was extracted with CH_2Cl_2 (3 times), The organic phases were dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (47 mg, 19 mmol) as a colorless oil (94 % yield).

TLC: R_f 0.4 (EtOAc/hexane, 1/2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 5.68 (ddq, *J* = 15.3, 6.3, 1.3 Hz, 1H), 5.45 (ddq, *J* = 15.3, 7.8, 1.5 Hz, 1H), 4.57 (d, *J* = 5.4, 2H), 4.10-4.04 (m, 1H), 3.63 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.46 (dd, *J* = 9.3, 7.2 Hz, 1H), 3.28 (br, 2H), 1.74-1.68 (m, 1H), 1.71 (dd, *J* = 6.3, 1.5 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 132.3, 128.6, 128.5, 127.8, 127.7, 75.0, 73.4, 72.7, 41.0, 29.7, 17.7, 12.8. HRMS Calcd. for $C_{15}H_{22}O_3$ (M+1): 251.1647, Found: 251.1648. FTIR (NaCl film): 3385, 3029, 2918, 1720, 1496, 1453, 1376, 1326, 1101, 1005, 968, 927, 738, 698 cm^{-1}.

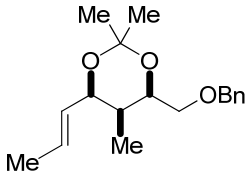
^{1}H NMR



^{13}C NMR



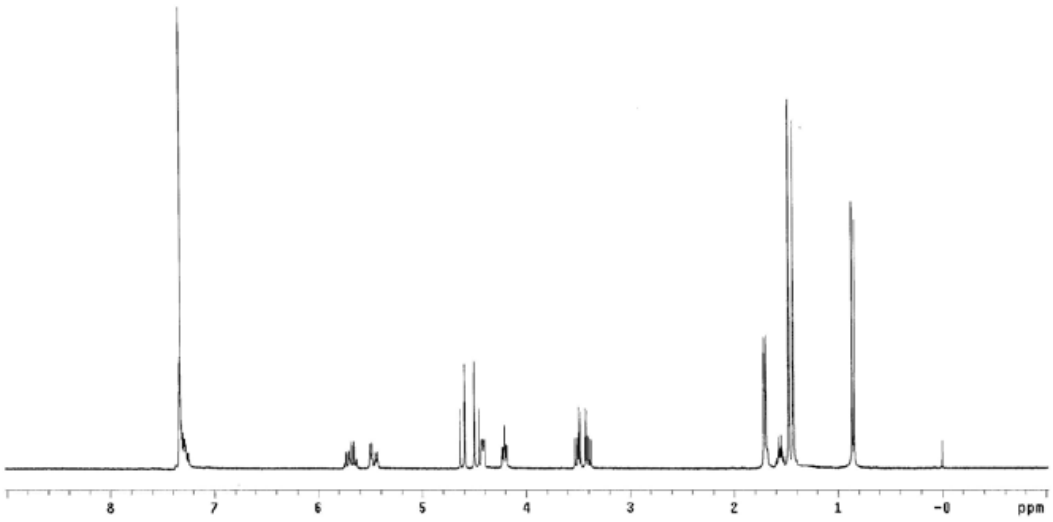
4-Benzyloxymethyl-2,2,5-trimethyl-6-propenyl-[1,3]dioxane



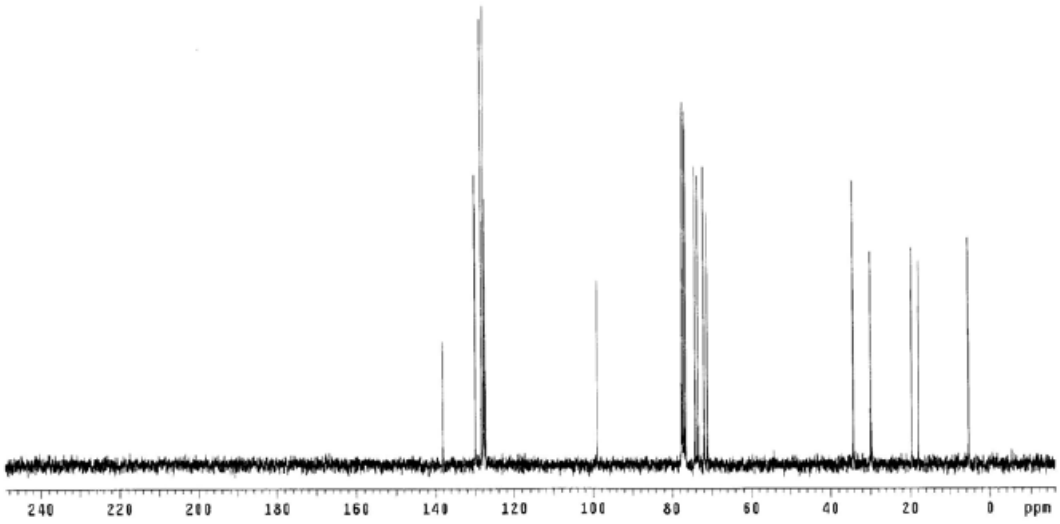
To a solution of 1-benzyloxy-3-methyl-hept-5-ene-2,4-diol **2.6a** (54 mg, 0.22 mmol, 100 mol%) in 2,2-dimethoxypropane (5 mL) at 0 ^{o}C was added *p*-TsOH•H_2O (2 mg, 0.01 mmol, 5 mol%). After 3 hours at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ (aq.), extracted with EtOAc (3 times), The organic phases were dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (58 mg, 0.20 mmol) as a colorless oil (91 % yield).

TLC: R_f 0.6 (EtOAc/hexane, 1/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 5.70 (ddq, *J* = 15.3, 6.6, 1.2 Hz, 1H), 5.47 (ddq, *J* = 15.3, 6.3, 1.5 Hz, 1H), 4.62 (d, *J* = 12, 1H), 4.48 (d, *J* = 12, 1H), 4.42 (ddd, *J* = 6.3, 5.7, 1.2, 1H), 4.21(ddd, *J* = 6.6, 6.3, 2.4, 1H), 3.50 (dd, *J* = 9.9, 6.6, 1H), 3.41 (2.85 (dd, *J* = 9.9, 6.3, 1H), 1.71 (dd, *J* = 6.6, 1.5 Hz, 3H), 1.59-1.48 (m, 1H), 1.48 (s, 3H), 1.43(s, 3H), 0.92 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 129.9, 128.3, 127.7, 127.6, 127.3, 99.0, 74.0, 73.4, 71.8, 70.9, 34.3, 29.9, 19.6, 17.8, 5.4. HRMS Calcd. for $C_{18}H_{26}O_3$ (M+1): 291.1960, Found: 291.1962. FTIR (NaCl film): 2989, 2936, 1453, 1379, 1254, 1199, 1176, 1103, 1075, 1012, 967, 938, 735, 697 cm^{-1}.

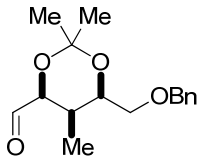
^{1}H NMR



^{13}C NMR



6-Benzyloxymethyl-2,2,5-trimethyl-[1,3]dioxane-4-carbaldehyde

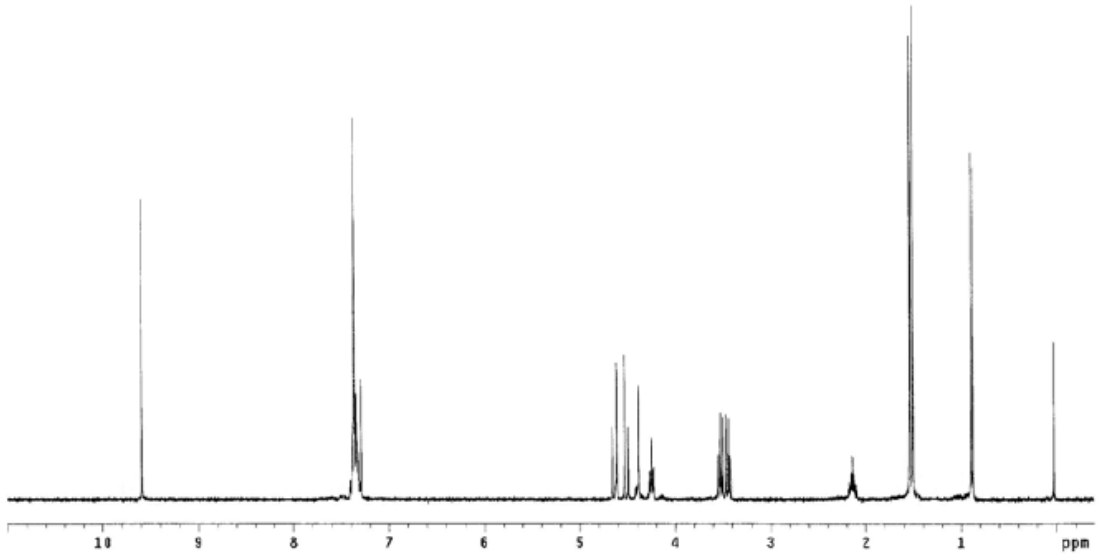


2.6c

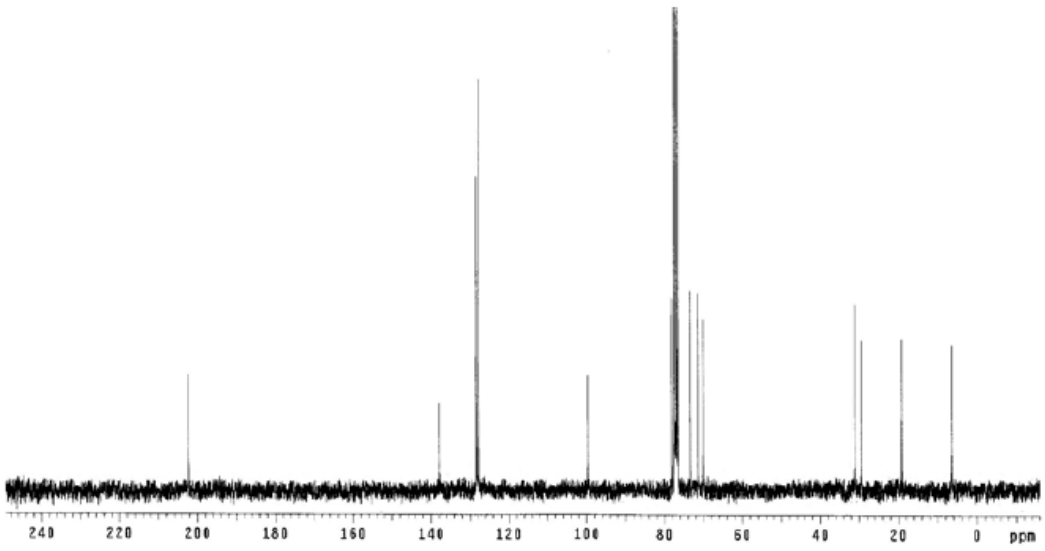
A solution of 4-benzyloxymethyl-2,2,5-trimethyl-6-propenyl-[1,3]dioxane (47 mg, 0.16 mmol, 100 mol%) in CH_2Cl_2 (30 mL) at -78 ^oC was bubbled with O_3 until blue color persisted. N_2 was bubbled for 10 min and PPh_3 (47 mg, 0.18 mmol, 113 mol%) was added to the reaction mixture, and stirred the reaction mixture overnight at ambient temperature. The reaction mixture was evaporated, and the residue was purified by flash chromatography (SiO_2: EtOAc/hexane) to afford the title compound (33 mg, 0.12 mmol) as a colorless oil (74 % yield).

TLC: R_f 0.2 (EtOAc/hexane, 1/3). ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.38-7.29 (m, 5H), 4.63 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.38 (d, J = 3.0 Hz, 1H), 4.25 (ddd, J = 6.6, 6.3, 2.4 Hz, 1H), 3.53 (dd, J = 9.6, 6.3 Hz, 1H), 3.44 (dd, J = 9.6, 6.6 Hz, 1H), 2.14 (ddq, J = 6.6, 3.0, 2.4 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2, 137.9, 128.4, 127.7, 99.7, 78.2, 73.5, 71.3, 70.1, 31.2, 29.5, 19.1, 6.3. HRMS Calcd. for $C_{16}H_{22}O_4$ (M+1): 279.1596, Found: 279.1598. FTIR (NaCl film): 3454, 2933, 2869, 2359, 1720, 1626, 1453, 1374, 1274, 1201, 1099, 739, 698 cm^{-1}.

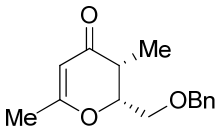
^{1}H NMR



^{13}C NMR



2-Benzyloxymethyl-3,6-dimethyl-2,3-dihydro-pyran-4-one

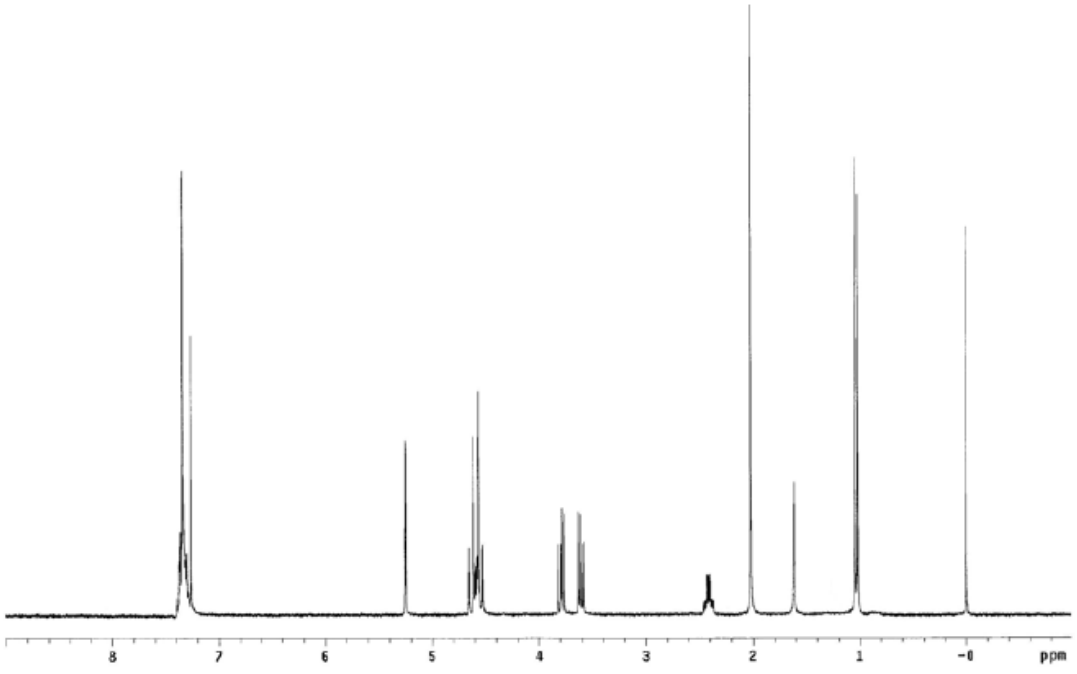


2.6d

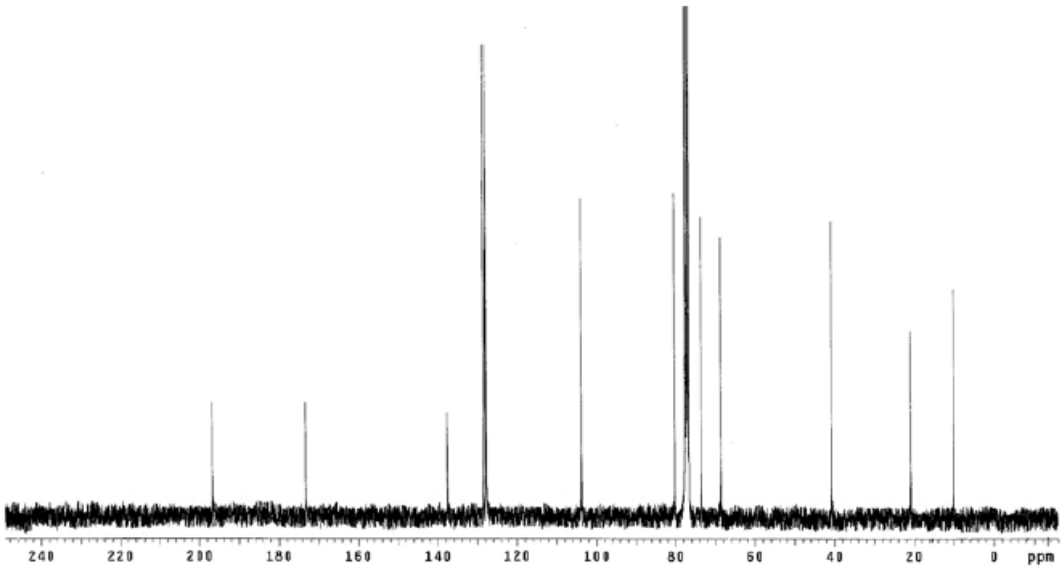
A 25 mL Schlenk tube was charged with $PdCl_2$ (7 mg, 0.04 mmol, 10 mol%), CuCl (4 mg, 0.04 mmol, 10 mol%), and Na_2HPO_4 (7 mg, 0.04 mmol, 10 mol%) and evacuated and backfilled with oxygen (3 times, balloon). A solution of the enone **2.3b** (100 mg, 0.40 mmol, 100 mol%) in DME (3 mL) was added via cannula. The resulting mixture was heated to 50 ^oC and allowed to stir at this temperature for 12 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with Et_2O and filtered through a pad of silica, and concentrated in vacuo to give a crude residue that was further purified by flash column chromatography (SiO_2: EtOAc/hexane) to afford the title compound (70 mg, 0.28 mmol) as a colorless oil (71 % yield).

TLC: R_f 0.3 (EtOAc/hexane, 1/3). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.30 (m, 5H), 5.26 (s, 1H), 4.66-4.53 (m, 3H), 3.61 (dd, J = 10.5, 4.5 Hz, 1H), 3.79 (dd, J = 10.5, 7.2 Hz, 1H), 2.41 (dq, J = 7.2, 3.6 Hz, 1H), 2.02 (s, 3H), 1.03 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6, 173.3, 137.5, 128.5, 127.9, 127.7, 103.7, 80.2, 73.5, 68.7, 40.8, 20.8, 10.0. HRMS Calcd. for $C_{15}H_{18}O_8$ (M+1): 247.1344, Found: 247.1346. FTIR (NaCl film): 2919, 2360, 1668, 1610, 1453, 1393, 1337, 1240, 1175, 1090, 970, 827, 739, 697 cm^{-1}.

^{1}H NMR



^{13}C NMR



General Procedure for Asymmetric Aldol Coupling of Enones and Aldehydes

To a 13 mm × 100 mm test-tube were added Li_2CO_3 (10 mol%), [Rh(cod)(AP-I)$_2$]OTf (5 mol%), aldehyde (100 mol%) and DCM (1.0 M). The test-tube was sealed, cooled to 0 ^oC and the reaction system was sparged with Ar (g) followed by H_2 (g) for 20 seconds each. The reaction system was placed under one atmosphere of hydrogen using a balloon and enone (300 mol%) was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h at 0 ^oC. The reaction mixture was evaporated and the aldol products were separated by flash chromatography (SiO2: EtOAc/Hexane).

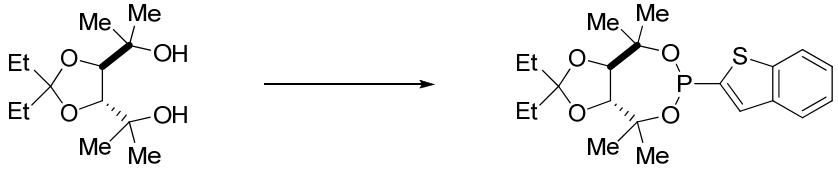
General Procedure for the determination of Enantiomeric Excess

Enantioselectivities were determined by chiral stationary phase HPLC analyses made in comparison to racemic diastereomeric mixtures prepared by (i) hydrogenation of the corresponding Morita-Baylis-Hillman adducts, or in the case of the ethyl vinyl ketone adducts (ii) the aldol reaction between the lithium enolate of 3-pentanone and the corresponding aldehyde, followed by treatment with magnesium bromide etherate. The enantiomeric excess reported for all products is based on the average of two reactions, with a minimum of two HPLC analyses per reaction (averaged). In all cases the enantiomeric excess did not vary more than 2% between runs.

General Procedure for the Synthesis of Racemic Diastereomeric Mixtures of Aldol Products

Aldehyde (1.0 mmol, 100 mol%), enone (3 mmol, 300 mol%), and DABCO (12 mg, 0.10 mmol, 10 mol%) were dissolved in THF (0.1 M) and stirred at 25 ^{o}C for 12 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (SiO_2: EtOAc/Hexane). The MBH adduct (0.50 mmol, 100 mol%) was dissolved in EtOAc (0.1 M) and 10% Pd-C (10 wgt%) was added. The reaction vessel was flushed with H_2 (g) and the mixture was stirred for 8 h at 25 ^{o}C. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (SiO2: EtOAc/Hexane) to give the racemic aldol adducts as diastereomeric mixtures in variable yields (20-70% over 2 steps).

Representative procedure for the synthesis of Chiral Ligands

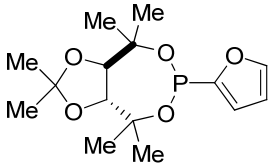


To a solution of (4*R*,5*R*)-diethyl- 2,2-dimethyl-1,3-dioxolane-4,5-dipropan-2-ol (4.0 g, 16.2 mmol, 100 mol%) and triethylamine (6.8 mL, 48.6 mmol, 300 mol%) in THF (0.1 M) at -78 ^{o}C, PCl_3 (2.2 mL, 20.0 mmol, 120 mol%) was added quickly with stirring, and the reaction was allowed to come to 25 ^{o}C over 1 hour, and then was stirred for 10 hours at 25 ^{o}C. The reaction was then filtered through a plug of celite under an argon atmosphere with the exclusion of moisture, and the solvent was removed via distillation

at reduced pressure. The crude solid was then dissolved in 50 mL of ether, and the solids were removed by filtration through a plug of celite under an argon atmosphere with the exclusion of moisture. The solvent was again removed under reduced pressure. The resulting oil (3a*R*,8a*R*)-6-chloro-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4.9 g, 15.8 mmol) was of sufficient purity to be used directly in the next step.

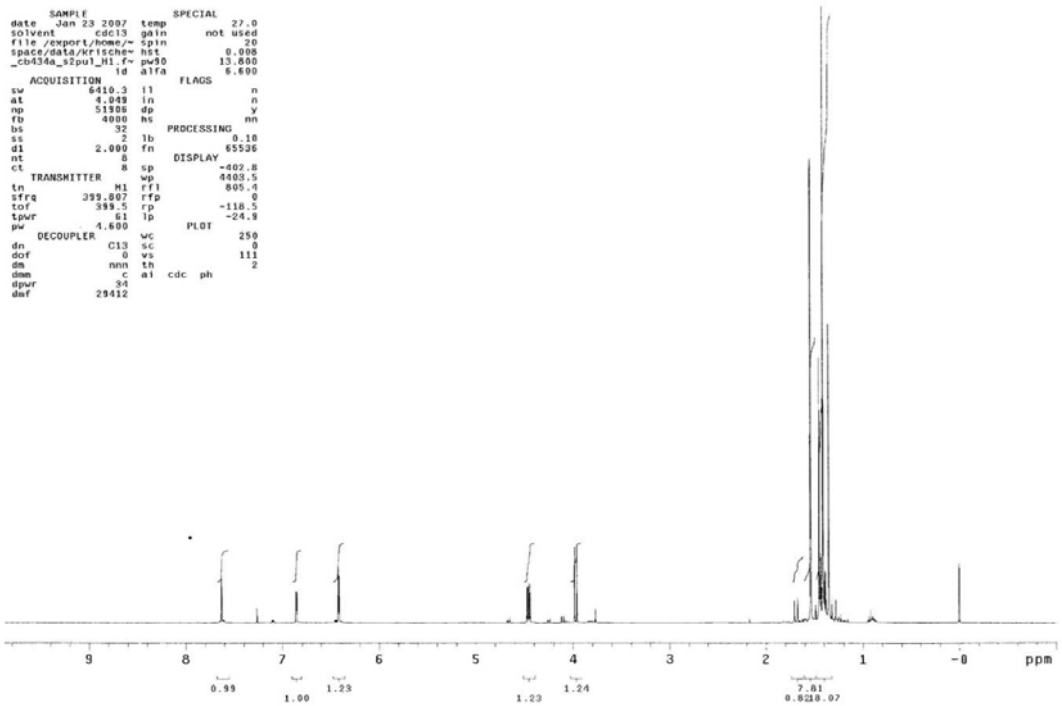
To benzothiophene (1.65 g, 12.3 mmol, 100 mol%) dissolved in THF (0.1 M) and cooled to -78 ^{o}C, *tert*-butyllithium (1.2 M, 10.2 mL, 12.2 mmol, 100 mol%) was added dropwise and the mixture was stirred for 1 hour at -78 ^{o}C. This solution was then transferred via cannula quickly to a solution of (3a*R*,8a*R*)-6-chloro-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4.9 g, ~15.8 mmol, 100 mol%) in THF (0.1 M) at -78 ^{o}C. The reaction was allowed to warm to 25 ^{o}C over 1 hour, and then stirred for 10 hours at 25 ^{o}C. The solvent was then removed under reduced pressure and the crude product was purified by flash chromatography (SiO_2: Ether/Hexane) to give the title compound in 59% yield over 2 steps (3.88 g, 9.5 mmol).

(3a*R*,8a*R*)-6-(furan-2-yl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 1.4 Hz, 1H), 6.84-6.81 (m, 1H), 6.42–6.40 (m, 1H), 4.46 (dd, *J* = 9.2, 3.7 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 1.53 (s, 6H), 1.44 (s, 3H), 1.41 (s, 6H), 1.35 (S, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (d, *J* = 11.2 Hz), 146.7 (d, *J* = 4.5 Hz), 118.2 (d, *J* = 26.9 Hz), 110.1 (d, *J* = 5.2 Hz), 109.7, 82.5 (d, *J* = 3.7 HZ), 81.8 (d, *J* = 22.4 Hz), 76.5 (d, *J* = 4.5 Hz), 76.4 (d, *J* = 6.7 Hz), 29.9 (d, *J* = 3.0 Hz), 29.0 (d, *J* = 3.0 Hz), 27.3, 27.1, 23.2, 19.8 (d, *J* = 9.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 134.6. HRMS calcd for $C_{15}H_{24}O_5P$ (M+1): 315.1361, Found: 315.1366. FTIR (neat): 2980, 2936, 2884, 1456, 1370, 1243, 1560, 1071, 1041, 1010, 972, 926, 906, 883, 829, 750, 743 cm^{-1}. MP: 55-58 ^{o}C. $[\alpha]_D^{25}$ +12^{o}, c = 0.83 in DCM

^{1}H NMR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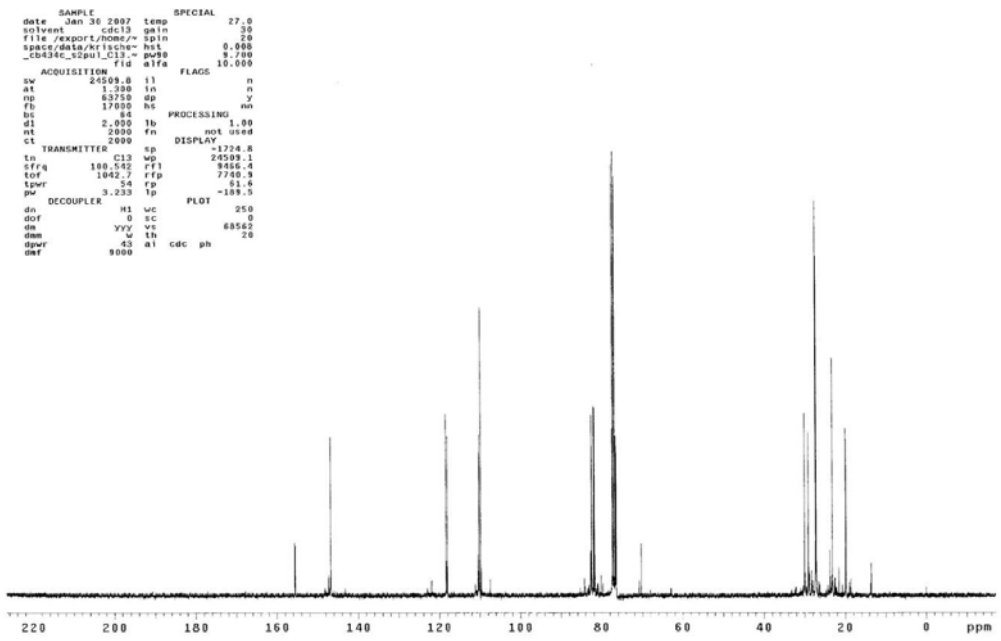
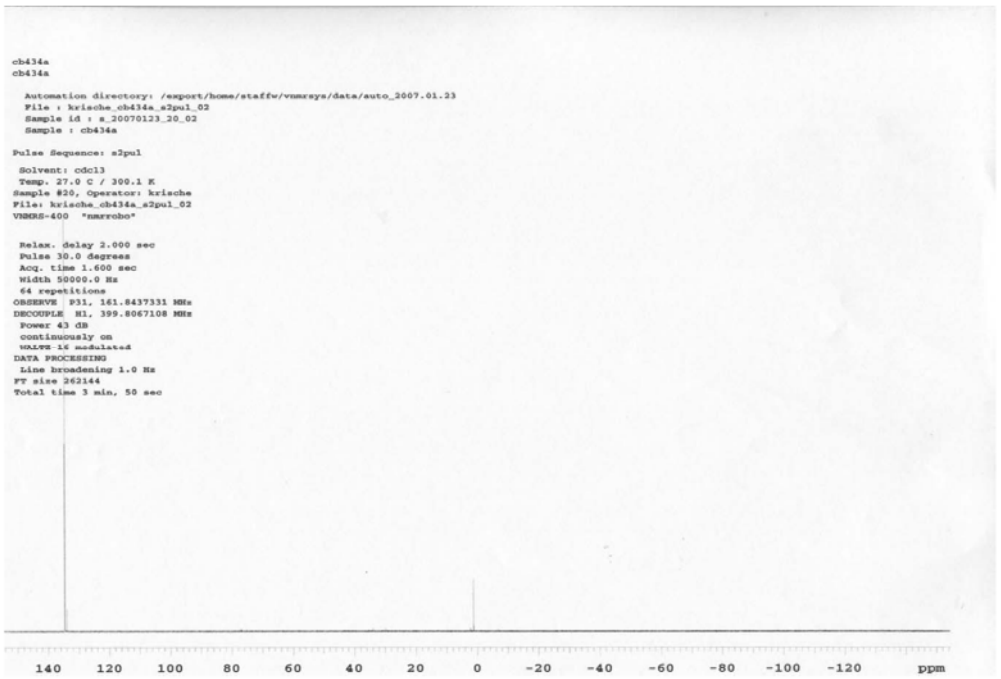
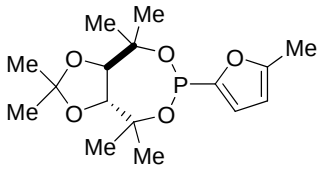
^{13}C NMR



^{31}P NMR

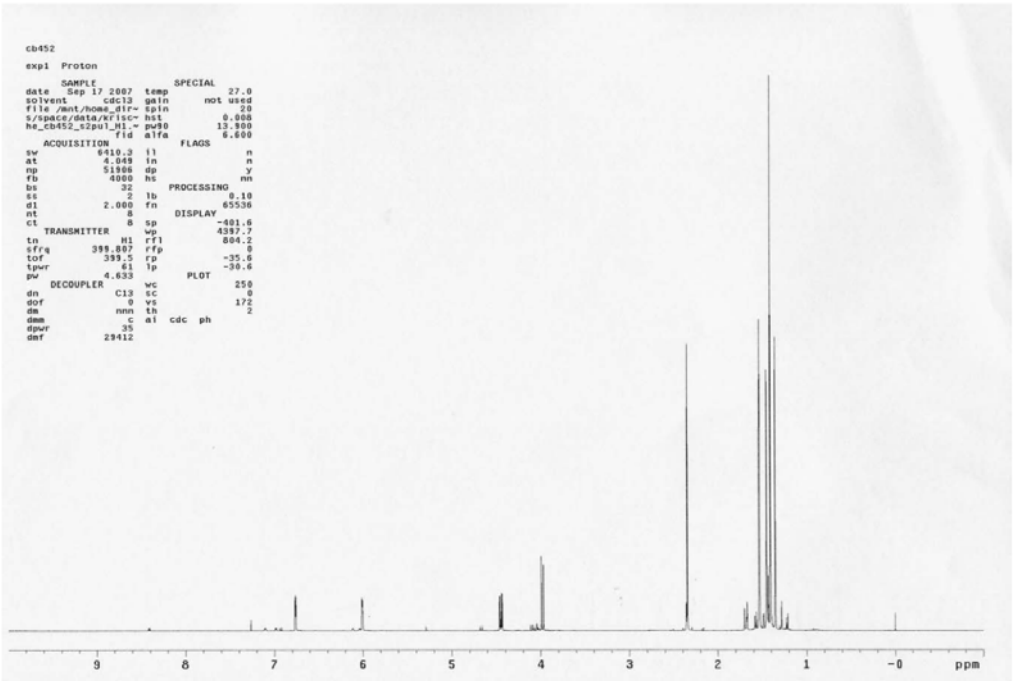


(3a*R*,8a*R*)-tetrahydro-2,2,4,4,8,8-hexamethyl-6-(5-methylfuran-2-yl)-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine]

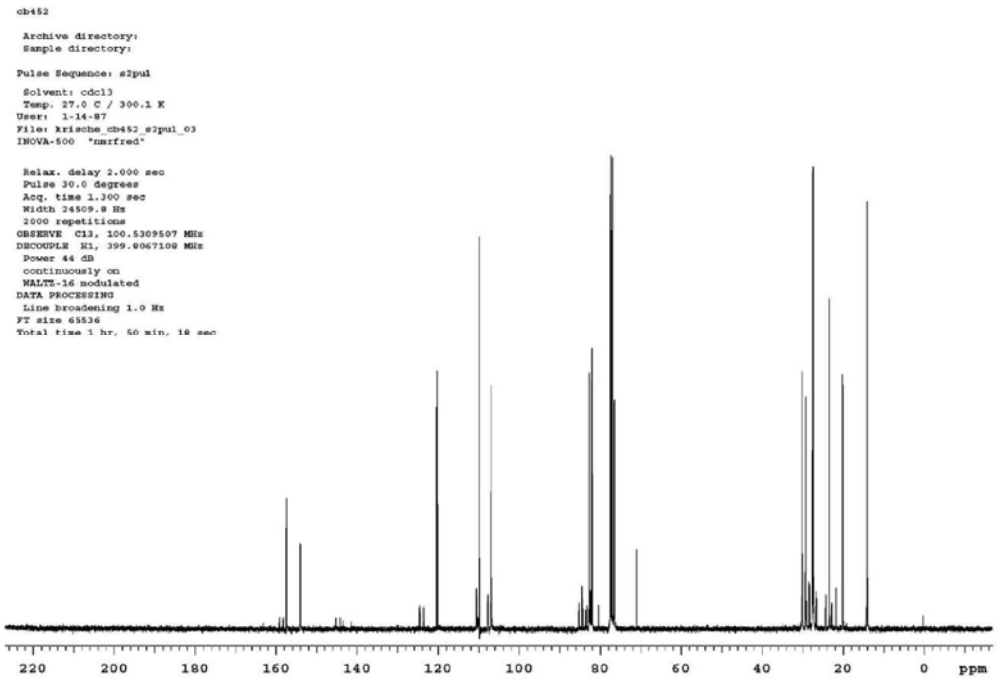


^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71-6.75 (m, 1H), 6.01-6.00 (m, 1H), 4.45 (d, *J* = 9.2, 3.7 Hz, 1H), 3.98 (d, *J* = 9.2 Hz, 1H), 2.35 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H), 1.41 (s, 6H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2 (d, *J* = 4.5 Hz), 153.7 (d, *J* = 10.5 Hz), 120.1 (d, *J* = 29.9 Hz), 109.6, 106.6 (6.7 HZ), 82.4 (d, *J* = 4.5 Hz), 81.8 (d, *J* = 22.4), 76.4 (d, *J* = 4.5 Hz), 76.2 (d, *J* = 6.0 Hz), 29.9 (d, *J* = 3.0 Hz), 29.0 (d, *J* = 3.0 Hz), 27.3, 27.1, 23.2, 19.8 (d, *J* = 10.5 Hz), 13.9. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 132.1. HRMS calcd for $C_{16}H_{26}O_5P$ (M+1): 329.1518, Found: 329.1520. FTIR (neat): 2986, 2935, 1508, 1374, 1242, 1169, 1145, 1078, 1015, 935, 878, 627 cm^{-1}. MP: 57-59 ^{o}C. $[\alpha]_D^{25}$ +5.0^{o}, c = 1.0 in DCM

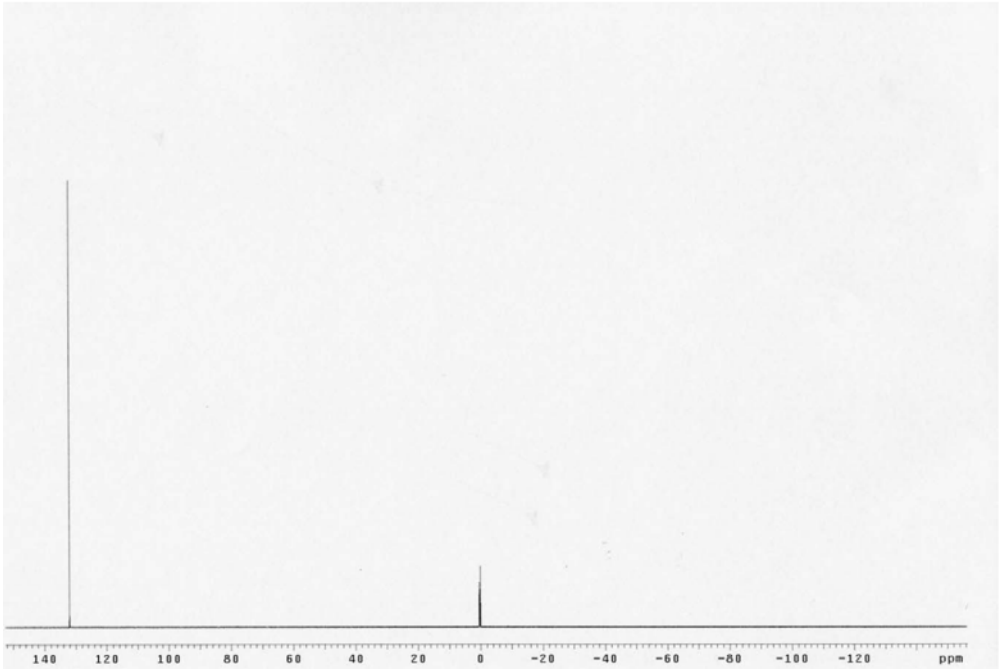
^{1}H NMR



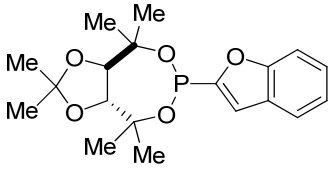
^{13}C NMR



^{31}P NMR



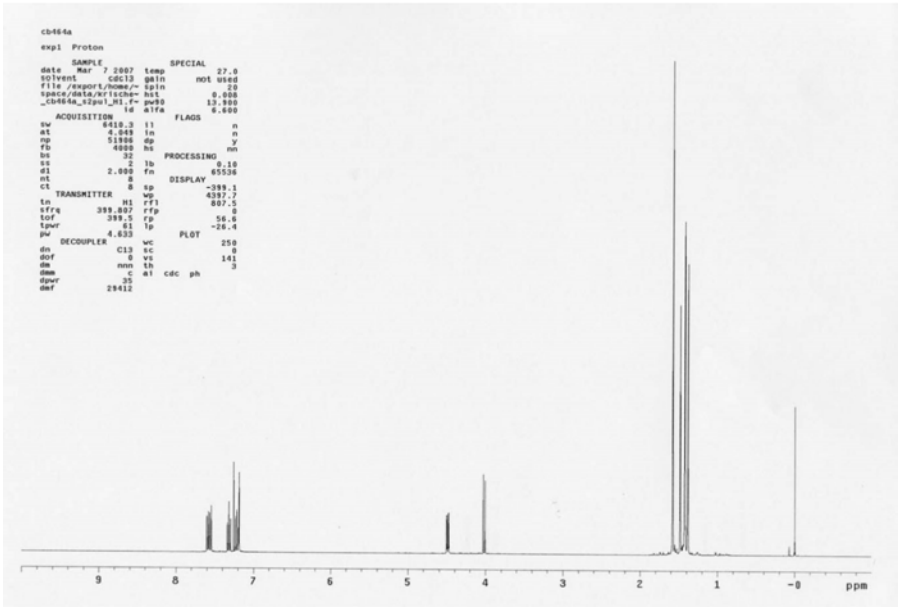
(3a*R*,8a*R*)-6-(benzofuran-2-yl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



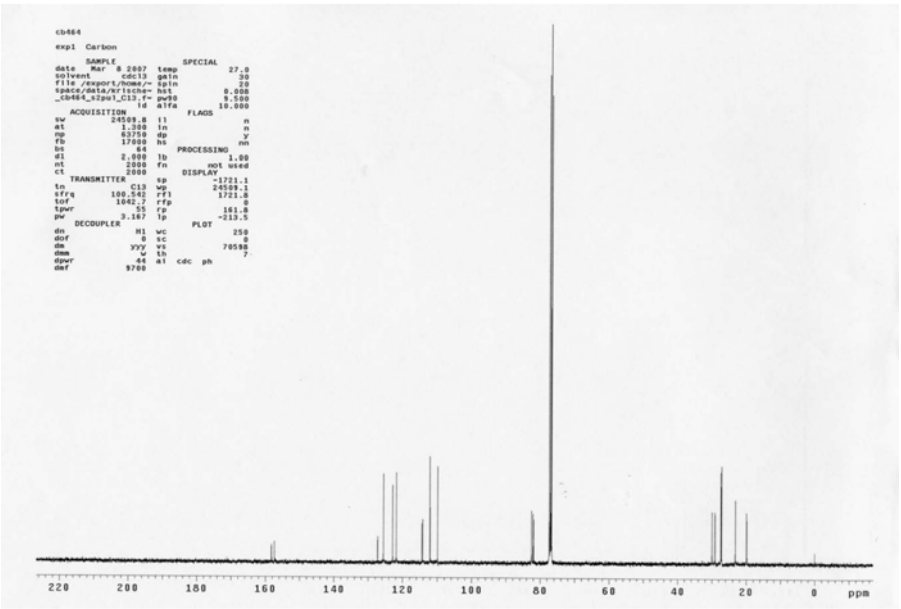
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dm, *J* = 7.8, 1H), 7.55 (dm, *J* = 8.2 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.24-7.18 (m, 2H), 4.49 (dd, *J* = 9.4, 3.7 Hz, 1H), 4.02 (d, *J* = 9.2 Hz, 1H), 1.58 (s, 6H), 1.48 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (d, *J* = 13.5 Hz), 157.3 (d, *J* = 3.7 Hz), 127.2 (d, *J* = 6.0 Hz), 125.6, 122.9, 121.8, 114.2 (d, *J* = 23.9 Hz), 112.0, 109.9, 82.5 (d, *J* = 4.5 Hz),

82.0 (J = 22.4 Hz), 30.0 (J = 3.0 Hz), 29.1 (d, J = 3.0 Hz), 27.4, 27.2, 23.2 (2C), 19.9, 19.8. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 136.8. HRMS calcd for $C_{19}H_{26}O_5P$ (M+1): 365.1518, Found: 365.1519. FTIR (neat): 2984, 2974, 1540, 1374, 1236, 1171, 1089, 979, 794, 753, 641 cm^{-1}. MP: 72–75 ^oC. $[\alpha]_D^{25}$ +12^o, c = 0.50 in DCM

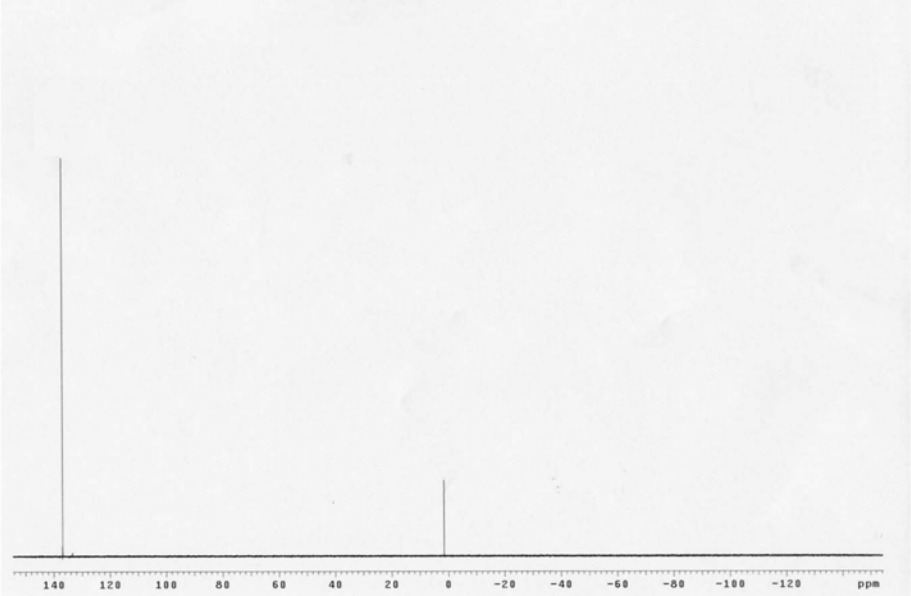
^{1}H NMR



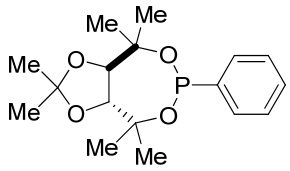
^{13}C NMR



^{31}P NMR



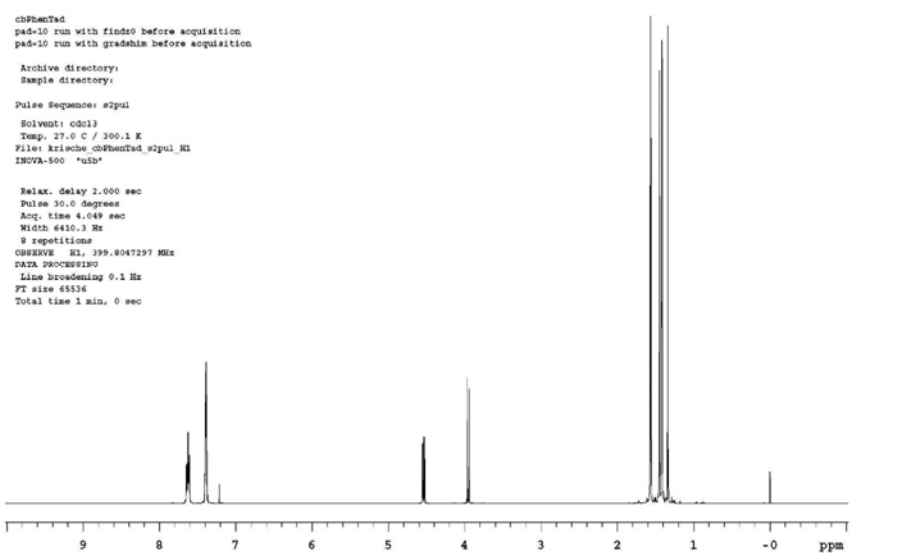
(3a*R*,8a*R*)-tetrahydro-2,2,4,4,8,8-hexamethyl-6-phenyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



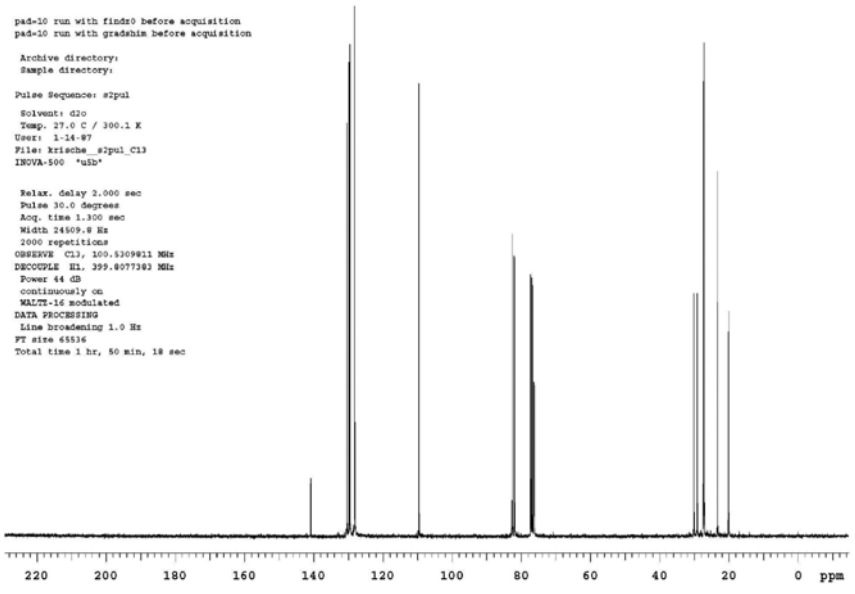
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (m, 2H), 7.40-7.37 (m, 3H), 4.54 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.95 (d, *J* = 9.2 Hz, 1H), 1.56 (s, 6H), 1.45 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9 (d, *J* = 6.0 Hz), 130.4, 129.7 (d, *J* = 23.9 Hz), 128.2 (d, *J* = 7.5 Hz), 109.6, 82.6 (d, *J* = 3.7 Hz), 82.0 (d, *J* = 22.4 Hz), 76.4 (d, *J* = 4.7 Hz), 76.2 (d, *J* = 5.2 Hz), 30.2 (d, *J* = 3.0 Hz), 29.1 (d, *J* = 3.0 Hz), 27.3, 27.2, 23.3 (2C), 20.1, 20.0. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 131.6. HRMS calcd for

$C_{17}H_{26}O_4P$ (M+1): 325.1569, Found: 325.1568. FTIR (neat): 2982, 2974, 1520, 11282, 1231, 1171, 1042, 997, 792, 638 cm^{-1}. MP: 62–64 ^oC. $[\alpha]_D^{25}$ +18^o, c = 0.4 in DCM

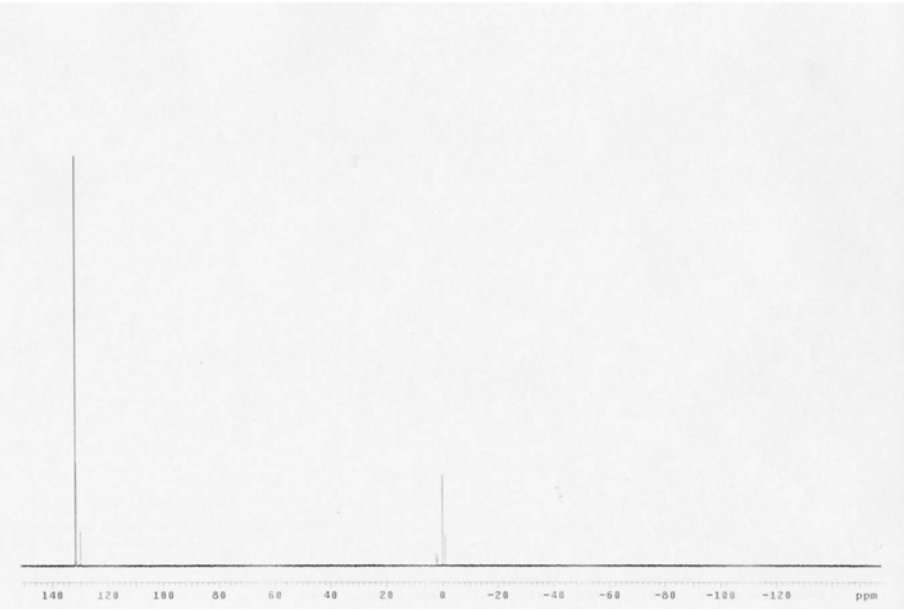
^1H NMR



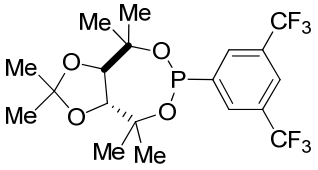
^{13}C NMR



^{31}P NMR



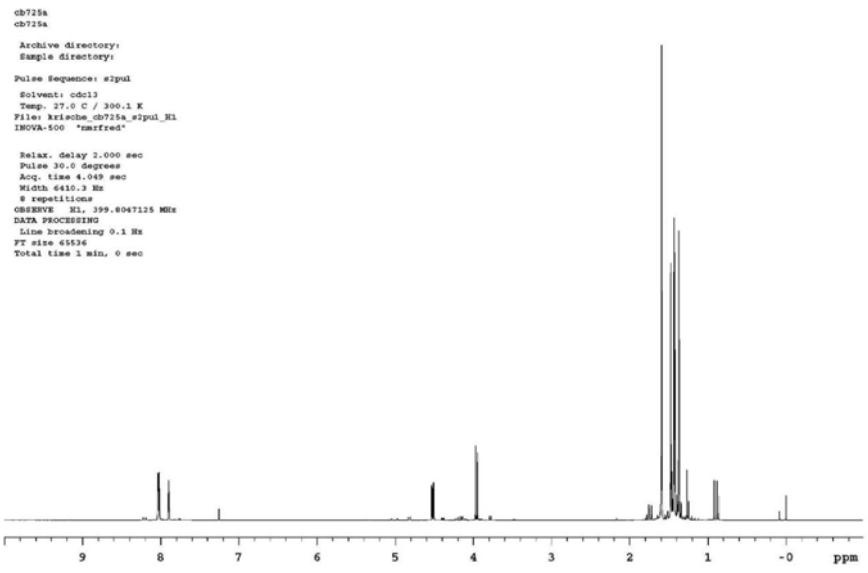
(3a*R*,8a*R*)-6-(3,5-bis(trifluoromethyl)phenyl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



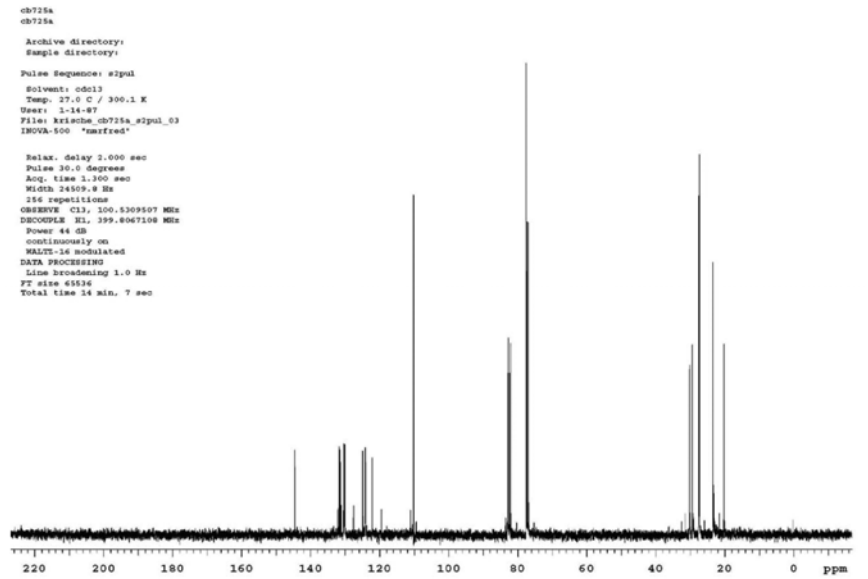
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.89 (s, 1H), 4.52 (dd, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 1.59 (s, 6H), 1.48 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4 (d, *J* = 14.2 Hz), 131.4 (qd, *J* = 33.7, 6.0 Hz, 2C), 130.0 (dm, *J* = 23.2 Hz, 2C), 124.0 (m), 123.3 (q, *J* = 273.0 Hz, 2C), 110.0, 82.6, 82.0 (d, *J* = 21.6 Hz), 77.3 (d, *J* = 3.7 Hz), 77.2 (d, *J* = 5.2 Hz), 30.0 (d, *J* = 3.0 Hz), 29.2 (d, *J* = 3.0 Hz), 27.3, 27.1, 23.2, 20.0 (d, *J* = 9.7 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 147.0.

HRMS calcd for $C_{19}H_{24}O_4F_6P$ (M+1): 461.1316, Found: 461.1287. FTIR (neat): 2988, 2940, 2896, 1456, 1372, 1280, 1136, 1078, 1016, 973, 936, 905, 835, 812, 742, 703, 682, 608 cm^{-1}. MP: 101-105 ^oC (dec). $[\alpha]_D^{25}$ +23^o, c = 0.83 in DCM

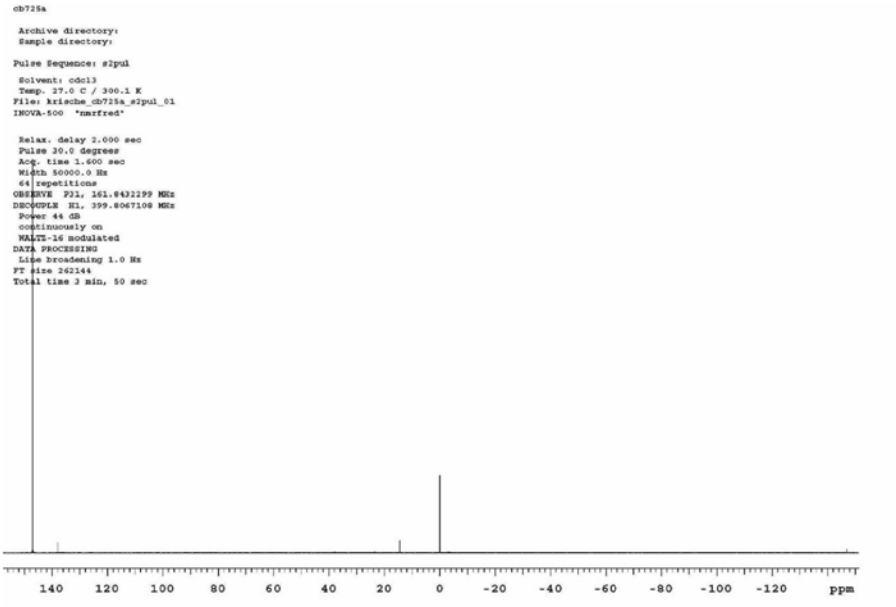
^1H NMR



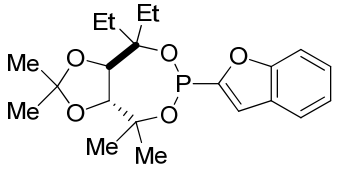
^{13}C NMR



^{31}P NMR



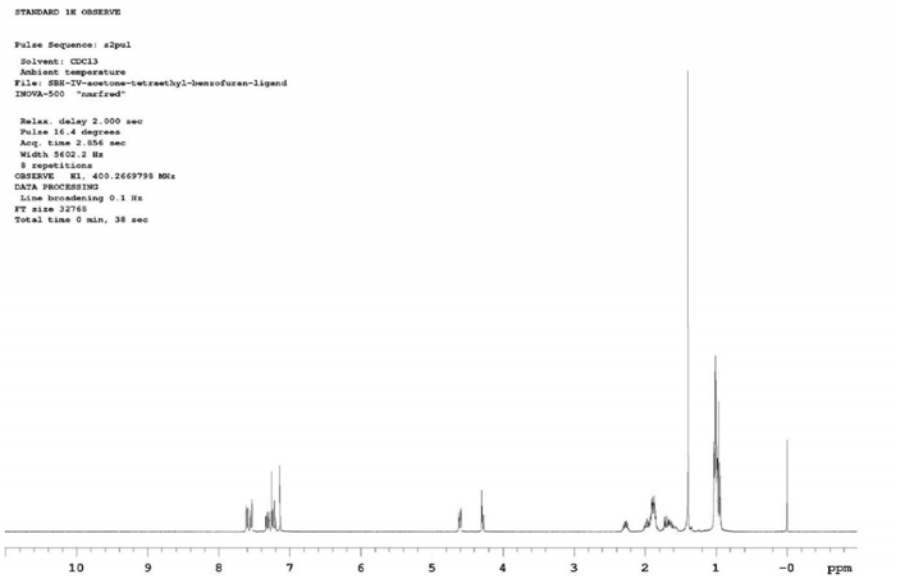
(3a*R*,8a*R*)-6-(benzofuran-2-yl)-4,4,8,8-tetraethyl-tetrahydro-2,2-dimethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



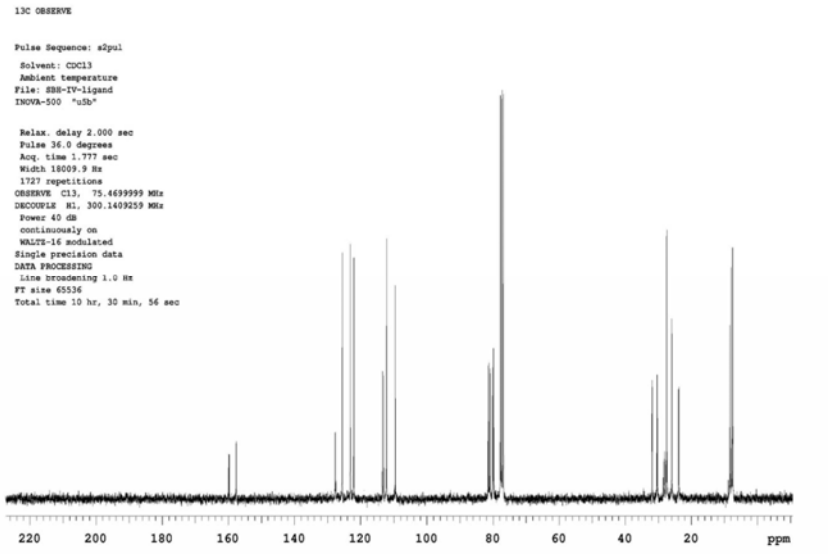
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.31 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.22 (td, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.14 (s, 1H), 4.61 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 2.32-2.24 (m, 1H), 2.03-1.82 (m, 5H), 1.75-1.55 (m, 2H), 1.39 (s,6H), 1.03-0.94 (m, 12H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.5 (d, *J* = 15.4 Hz), 157.3 (d, *J* = 4.4 Hz), 127.3 (d, *J* = 4.4 Hz), 125.2, 122.7, 121.7, 112.9 (d, *J* = 19.8 Hz), 111.9, 109.2, 81.1 (d, *J* = 17.7 Hz), 80.1 (d, *J* = 2.7

Hz), 79.8 (d, J = 2.7 Hz), 79.5 (d, J = 4.4 Hz), 31.6 (d, J = 5.0 Hz), 30.0 (d, J = 3.9 Hz), 27.3, 27.0, 25.6, 23.5 (d, J = 9.9 Hz), 8.0 (d, J = 1.7 Hz), 7.6, 7.2, 7.1 (d, J = 2.2 Hz). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 136.8. HRMS calcd for $C_{23}H_{34}O_5P$(M+1): 421.2144, Found: 421.2144. FTIR (neat): 2971, 2938, 2881, 1461, 1378, 1355, 1275, 1175, 1134, 1081, 1020, 974, 935, 840, 745, 724 cm^{-1}. MP: 54-56 ^{o}C. $[\alpha]_D^{25}$ +34.4, c = 1.13 in DCM

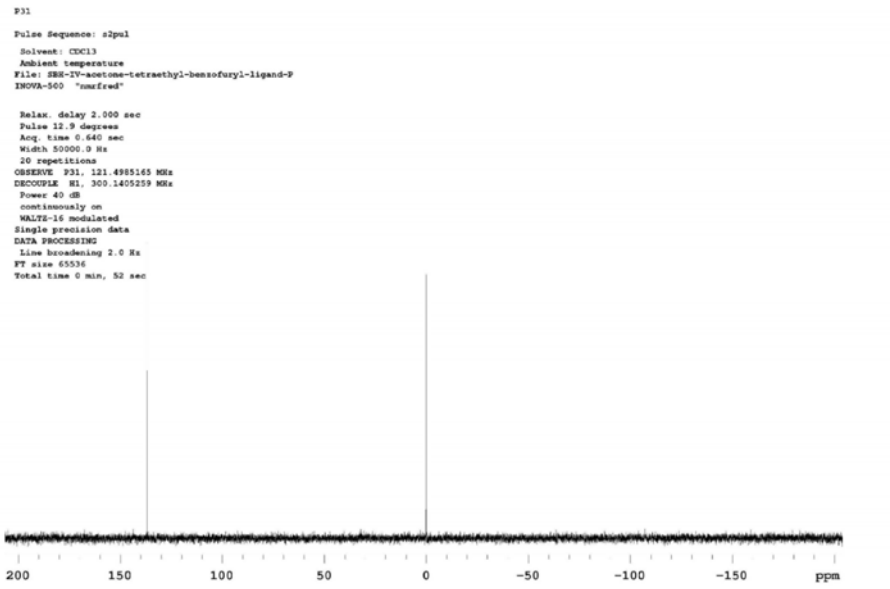
^{1}H NMR



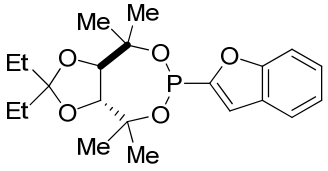
^{13}C NMR



^{31}P NMR



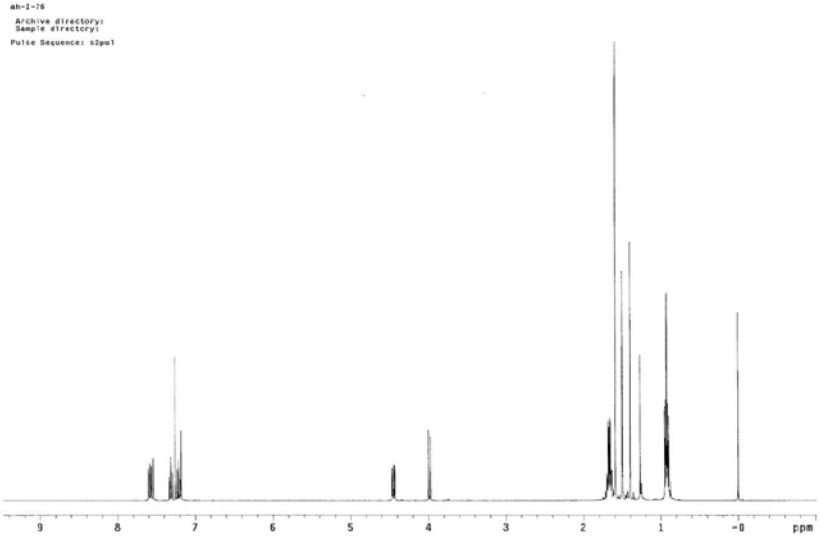
(3a*R*,8a*R*)-6-(benzofuran-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



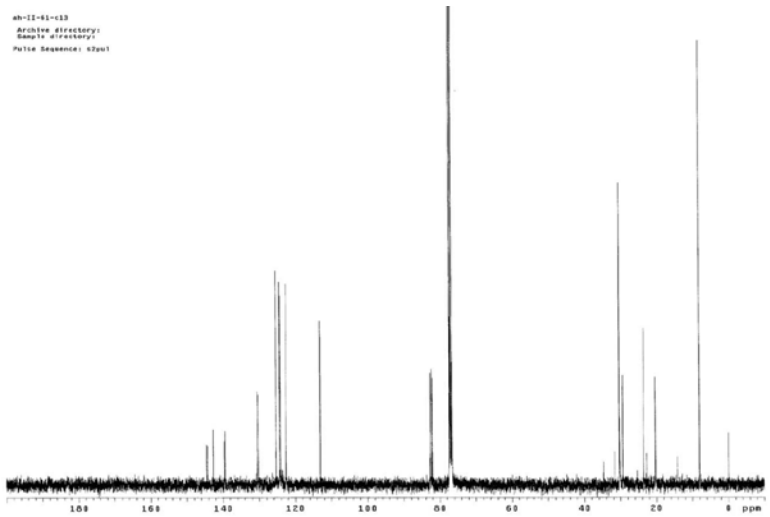
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.55, (ddd, *J* = 8.4, 1.8, 0.9 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3 Hz,1H), 7.22 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1H), 7.18 (dd, *J* = 1.3, 1.3 Hz, 1H), 4.44 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.98 (d, *J* = 9.4 Hz, 1H), 1.67 (q, *J* = 7.5 Hz, 2H), 1.66 (q, *J* = 7.5 Hz, 2H) 1.60 (s, 6H), 1.49 (s, 3H), 1.40 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3 (d, *J* = 13.4 Hz), 157.3 (d, *J* = 3.7 Hz), 127.2 (d, *J* = 5.2 Hz), 125.5, 122.9, 121.8, 114.2

(d, J = 24.7 Hz), 113.2, 112.0, 82.6 (d, J = 4.5 Hz), 82.1 (d, J = 22.4 Hz), 77.2 (d, J = 6.7 Hz, 2C), 30.2 (d, J = 10.4 Hz, 2C), 30.1 (d, J = 2.9 Hz), 29.3 (d, J = 2.9 Hz), 23.5, 20.2 (d, J = 10.5 Hz), 8.1 (d, J = 2.2 Hz, 2C). ^{31}P NMR (121 MHz, $CDCl_3$): δ 136.6. HRMS calcd for $C_{21}H_{30}O_5P$ (M+1): 393.1830, Found: 393.1831. FTIR (neat): 2976, 2939, 2881, 1535, 1463, 1449, 1383, 1368, 1253, 1157, 1078, 1008, 970, 938 cm^{-1}. $[\alpha]_D^{25}$ +196, c = 1.0 in DCM

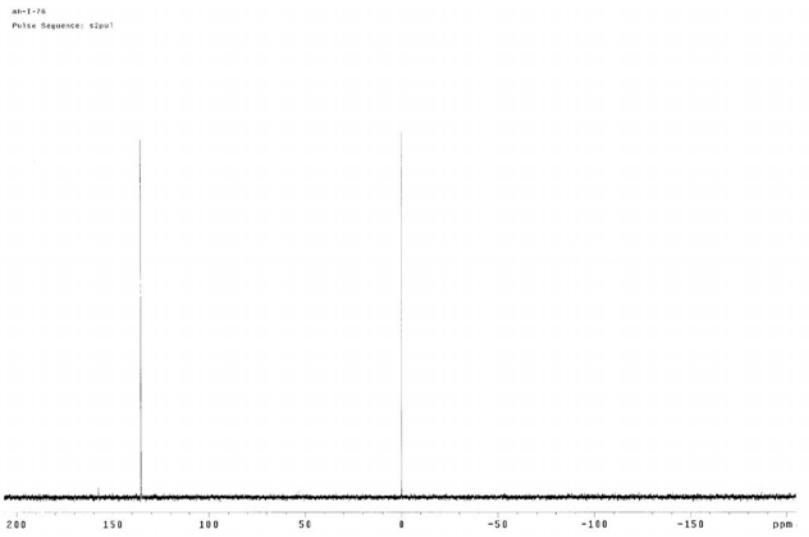
^{1}H NMR



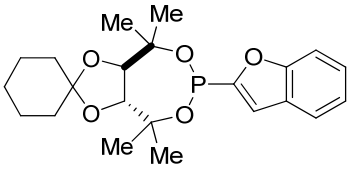
^{13}C NMR



^{31}P NMR



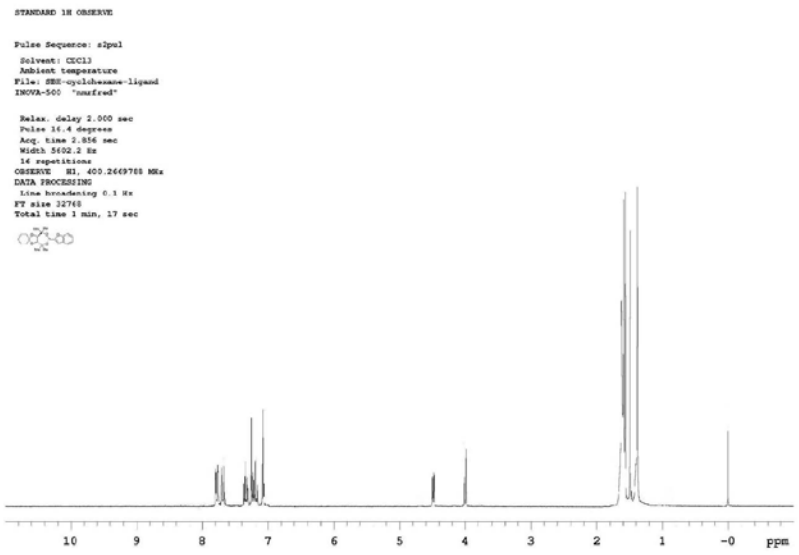
(3a*R*,8a*R*)-6-(benzofuran-2-yl)-2,2-cyclohexyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



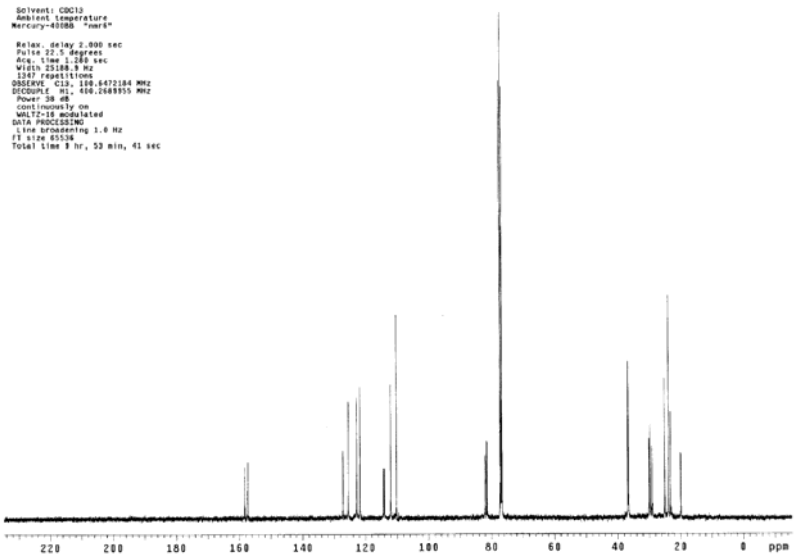
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.31 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.22 (td, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.14 (s, 1H), 4.48 (dd, *J* = 11.5 Hz, 5 Hz, 1H), 4.00 (d, *J* = 11.5 Hz, 1H), 1.62 – 1.55 (m, 16H), 1.37 (s, 6H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 158.2 (d, *J* = 13.8 Hz), 157.3 (d, *J* = 3.8 Hz), 127.2 (d, *J* = 5.3 Hz), 125.5, 122.8, 121.7, 114.1 (d, *J* = 23.8 Hz), 111.9, 110.2, 82.0 (d, *J* = 3.8 Hz), 80.6, 81.4, 77.0 (d, *J* = 6.1 Hz), 76.9 (d, *J* = 6.1 Hz), 36.7 (d, *J* = 9.2 Hz), 30.0 (d, *J* = 3.1 Hz), 29.7, 29.1 (d, *J* = 2.3 Hz), 25.0, 23.8, 23.2, 19.9 (d, *J* = 9.9 Hz). ^{31}P NMR

(121.5 MHz, $CDCl_3$): δ 135.6. HRMS calcd for $C_{22}H_{30}O_5P$(M+1): 405.1831, Found: 405.1833. FTIR (neat): 2933, 2856, 1445, 1384, 1368, 1278, 1253, 1159, 1144, 1122, 1090, 1059, 1009, 970, 945, 927, 826, 793, 743 cm^{-1}. MP: 90-92 ^oC. $[\alpha]_D^{25}$ -52.7, c = 0.97 in DCM.

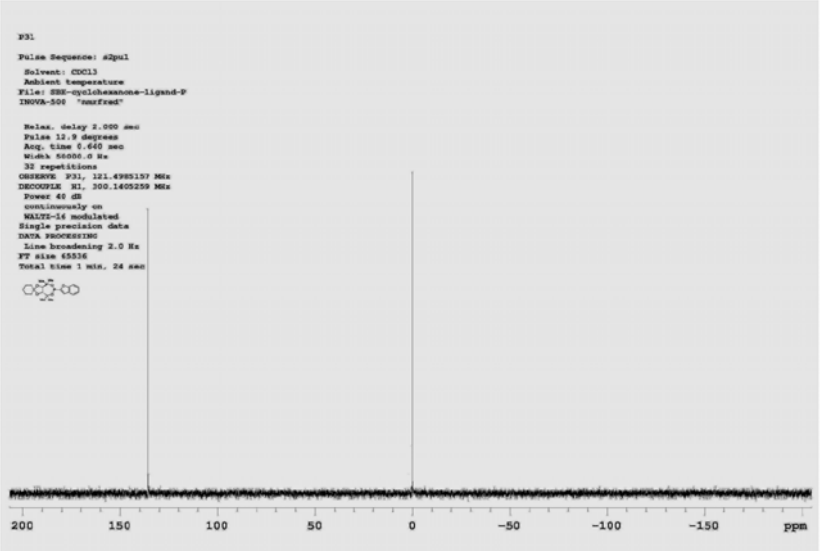
^1H NMR



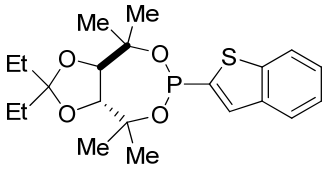
^{13}C NMR



^{31}P NMR



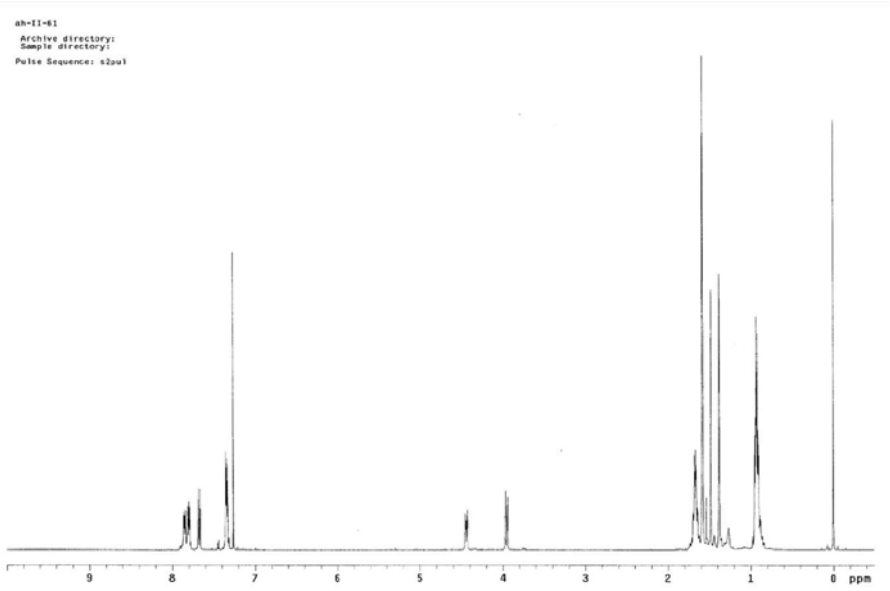
(3a*R*,8a*R*)-6-(benzo[b]thiophen-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



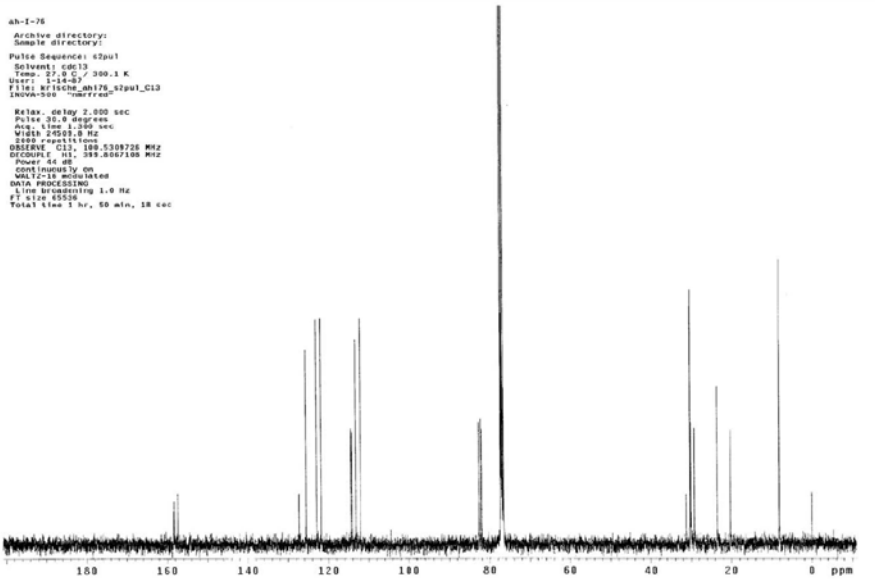
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.84 (m, 1H), 7.81-7.79 (m, 1H), 7.67 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.35-7.32 (m, 2H), 4.44 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.95 (d, *J* = 9.4 Hz, 1H), 1.68-1.64 (m, 4H), 1.58 (s, 6H), 1.48 (s, 3H), 1.38, (s, 3H), 0.95-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.4 (d, *J* = 26.2 Hz), 142.8, 139.6 (d, *J* = 10.47 Hz), 130.4 (d, *J* = 35.9), 125.3, 124.4, 124.3 (d, *J* = 23.2 Hz), 122.5, 113.1, 82.6 (d, *J* = 3.7 Hz), 82.0, 77.2, 77.1, 30.2 (d, *J* = 4.4 Hz, 2C) 29.3 (d, *J* = 2.2 Hz), 23.5, 20.4, 20.3, 8.1 (2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ 143.2. HRMS calcd for $C_{21}H_{30}O_4PS$ (M+1): 409.1602, Found:

409.1602. FTIR (neat) 3400, 2973, 2939, 1503, 1461, 1373, 1227, 1177, 1157, 1075, 1035, 1006, 969 cm^{-1}. MP: 66-69 °C. $[\alpha]_D^{25}$ +195, c = 1.0 in DCM

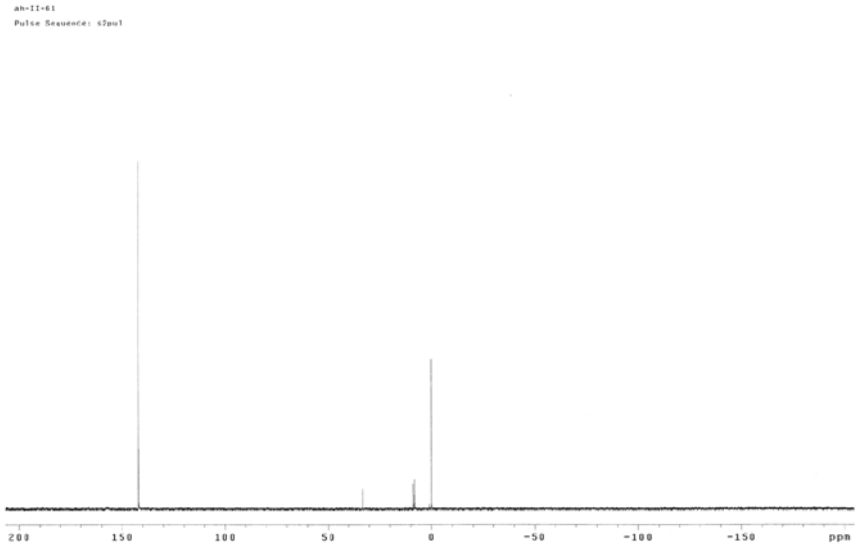
^{1}H NMR



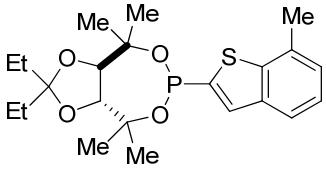
^{13}C NMR



^{31}P NMR



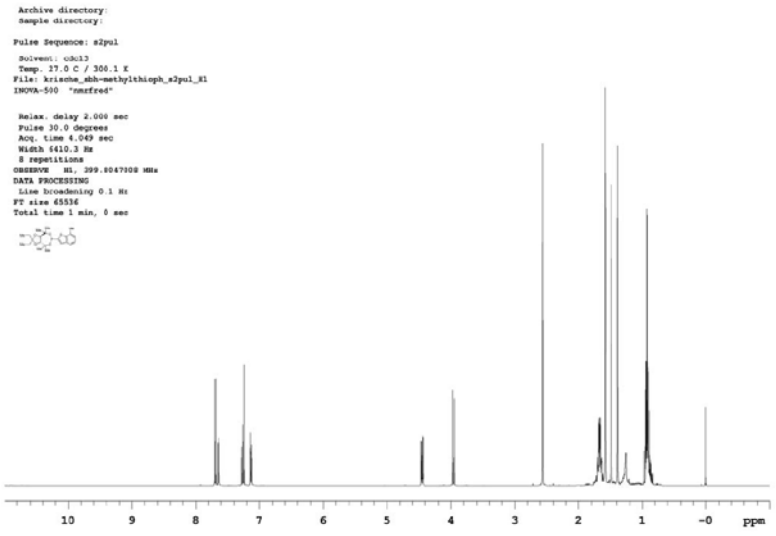
(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(7-methylbenzo[b]thiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



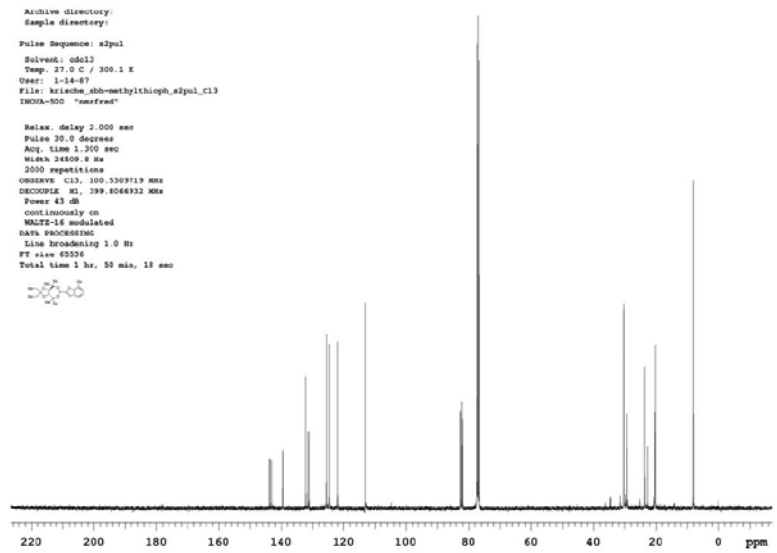
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.15-7.12 (m, 1H), 4.45 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 2.56 (s, 3H), 1.70-1.63 (m, 4H), 1.58 (s, 6H), 1.49 (s, 3H), 1.39, (s, 3H), 0.95-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 143.6 (d, *J* = 26.0 Hz), 143.0, 139.4 (d, *J* = 10.4 Hz), 132.1, 131.2 (d, *J* = 36.5 Hz), 125.4, 124.6, 122.0, 113.0, 82.6 (d, *J* = 3.7 Hz), 82.2, 82.0, 77.0 (d, *J* = 6.0 Hz), 30.3 (d, *J* = 3.0 Hz), 30.2 (d, *J* = 2.9 Hz), 29.3 (d, *J* = 2.9 Hz),

23.5, 22.6, 20.3 (d, J = 10.4 Hz), 20.3, 8.1 (2C). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 142.0. HRMS calcd for $C_{22}H_{31}O_4PS$ (M+1): 423.159, Found: 423.1755. FTIR (neat) 2975, 2938, 1463, 1383, 1367, 1157, 1079, 1061, 970, 939 cm^{-1}. $[\alpha]_D^{25}$ -7.6, c = 1.2 in DCM

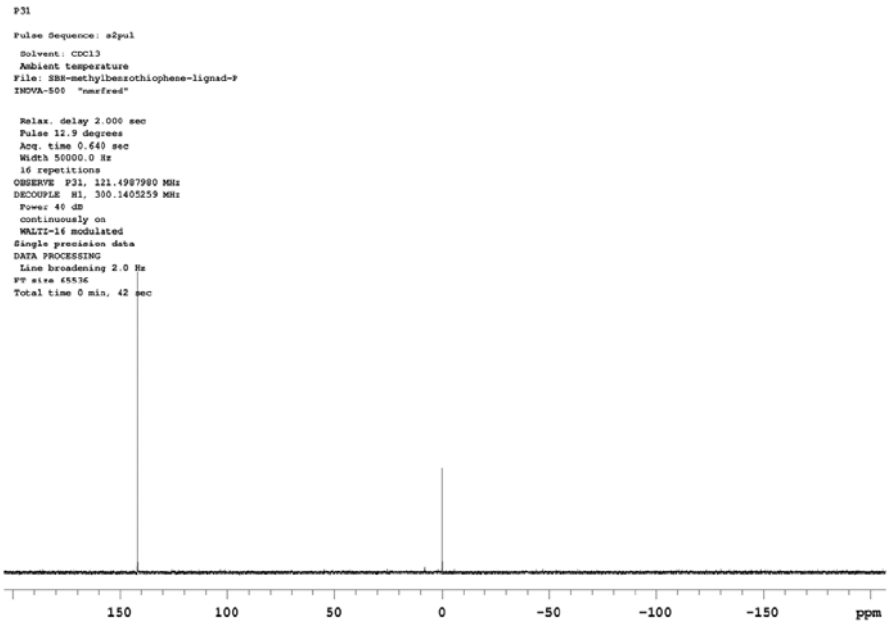
^{1}H NMR



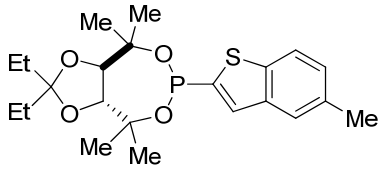
^{13}C NMR



^{31}P NMR



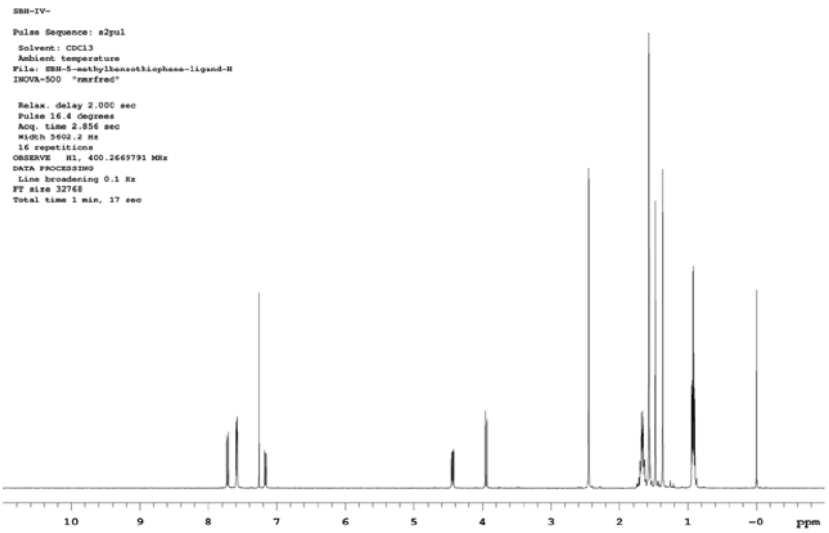
(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(5-methylbenzo[b]thiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine



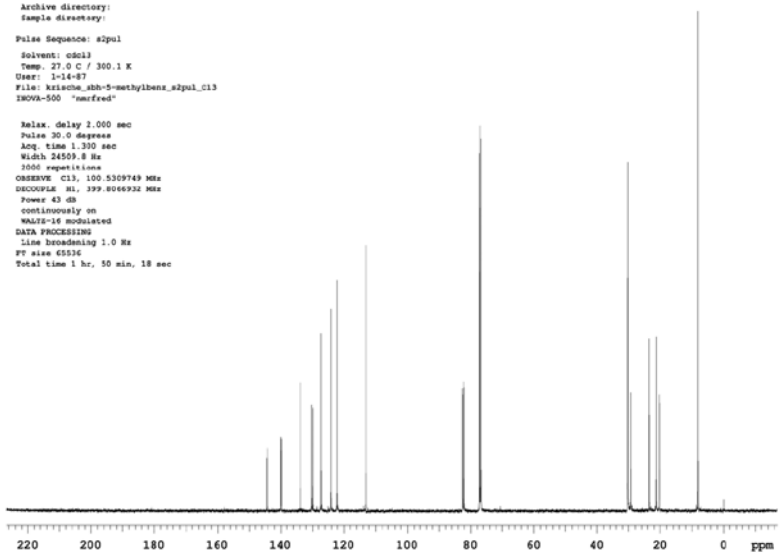
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 1H), 7.60-7.58 (m, 2H), 7.17 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 4.44 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 2.45 (s, 3H), 1.70-1.64 (m, 4H), 1.57 (s, 6H), 1.47 (s, 3H), 1.37, (s, 3H), 0.95-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.3 (d, *J* = 26.0 Hz), 140.0 (d, *J* = 16.3 Hz), 130.0 (d, *J* = 5.2 Hz), 133.8, 130.1 (d, *J* = 36.5 Hz), 127.2, 124.1, 122.1, 113.0, 82.6 (d, *J* = 3.8 Hz), 82.2, 82.0, 77.0 (d, *J* = 5.2 Hz), 30.2, 30.1, 29.3 (d, *J* = 3.0 Hz), 23.5, 21.3, 20.4, 20.3, 8.1 (2C). ^{31}P

NMR (121.5 MHz, $CDCl_3$): δ 142.1. HRMS calcd for $C_{22}H_{32}O_4PS$ (M+1): 423.1759, Found: 423.1764. FTIR (neat) 2975, 2937, 1463, 1383, 1368, 1157, 1079, 993, 970, 940 cm^{-1}. MP: 92-94 °C. $[\alpha]_D^{25}$ -10.54, c = 1.3 in DCM

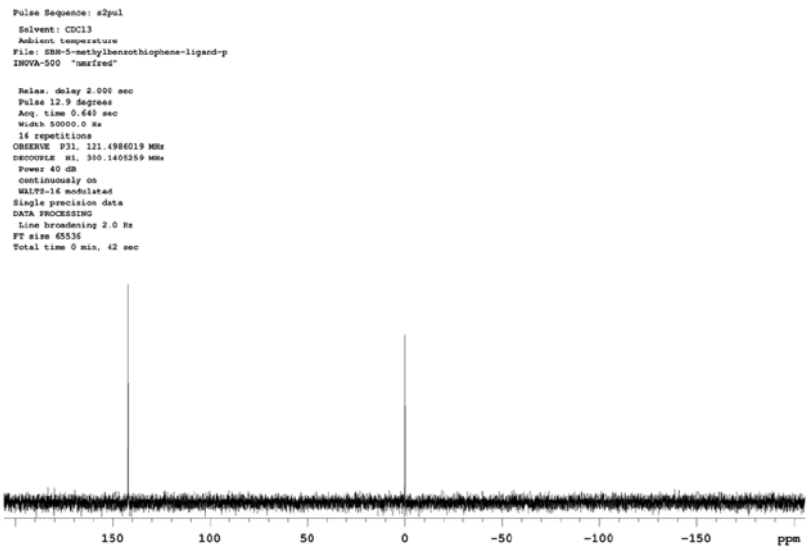
^1H NMR



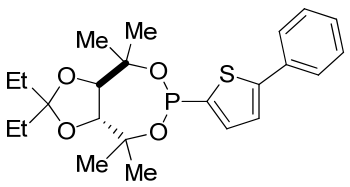
^{13}C NMR



^{31}P NMR



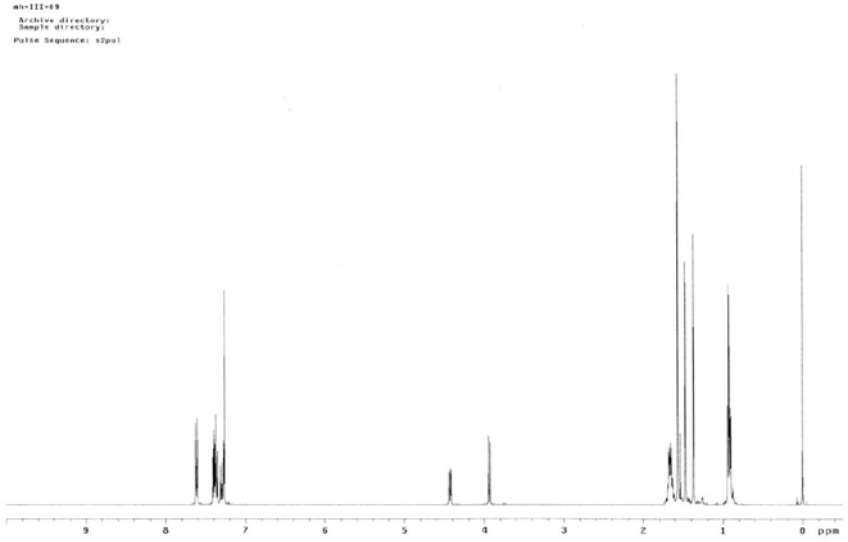
(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(5-phenylthiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine



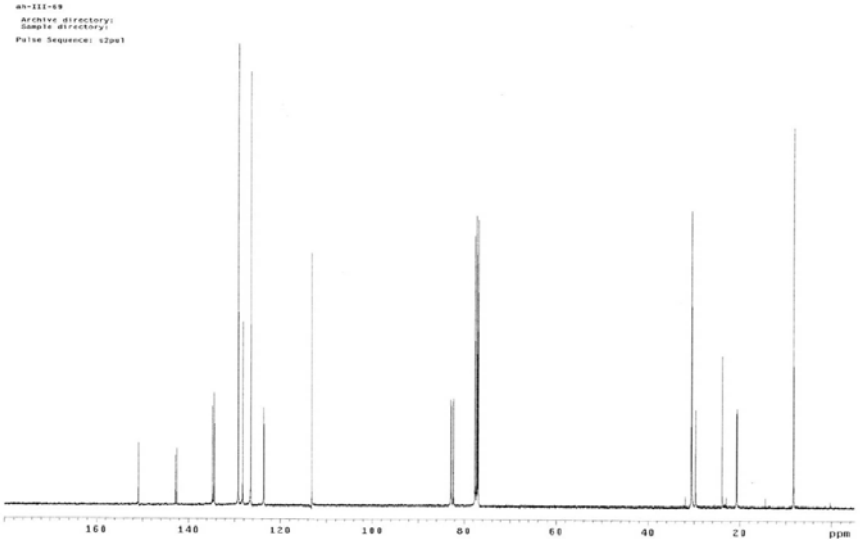
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (ddd, *J* = 7.6, 2.0, 0.8 Hz, 2H), 7.41-7.34 (m, 3H), 7.30 (ddd, *J* = 7.2, 1.2, 1.2 Hz, 1H), 7.27 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.43 (dd, *J* = 9.4, 3.3Hz, 1H), 3.94 (d, *J* = 9.4Hz, 1H), 1.66 (q, *J* = 2.9Hz, 2H), 1.66 (q, *J* = 3.5Hz, 2H), 1.56 (s, 6H), 1.47 (s, 3H), 1.37 (s, 3H), 0.93 (t, *J* = 7.4Hz, 3H), 0.92 (t, *J* = 7.4Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (d, *J* = 2.2Hz), 142.8, 142.6, 134.7, 134.4, 134.3, 129.1, 128.2, 126.5, 123.6 (d, *J* = 9.7Hz), 113.2, 82.9 (d, *J* = 3.7Hz), 82.3 (d, *J* = 21.7Hz), 77.1 (d, 2.2Hz), 77.1, 30.5 (2C), 30.5 (d, *J* = 5.2Hz), 29.6 (d, *J* = 3.0Hz), 23.8,

20.6 (d, J = 10.5Hz), 8.4 (2C). ^{31}P NMR (121.5) MHz, $CDCl_3$): δ 140.8. HRMS calcd for $C_{23}H_{32}O_4PS$ (M+1): 435.1756, Found: 435.1759. FTIR (neat): 3062, 2976, 2940, 2881, 1772, 1715, 1601, 1528, 1490, 1463, 1437, 1383, 1368, 1205, 1174, 1157 cm^{-1}. MP: 93-96 °C. $[\alpha]_D^{25}$ -3, c = 1.0 in DCM

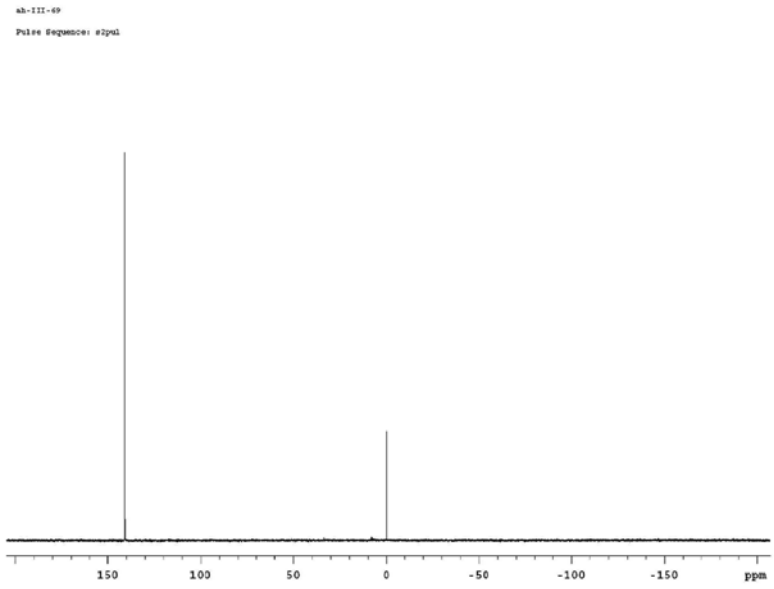
^{1}H NMR



^{13}C NMR



^{31}P NMR



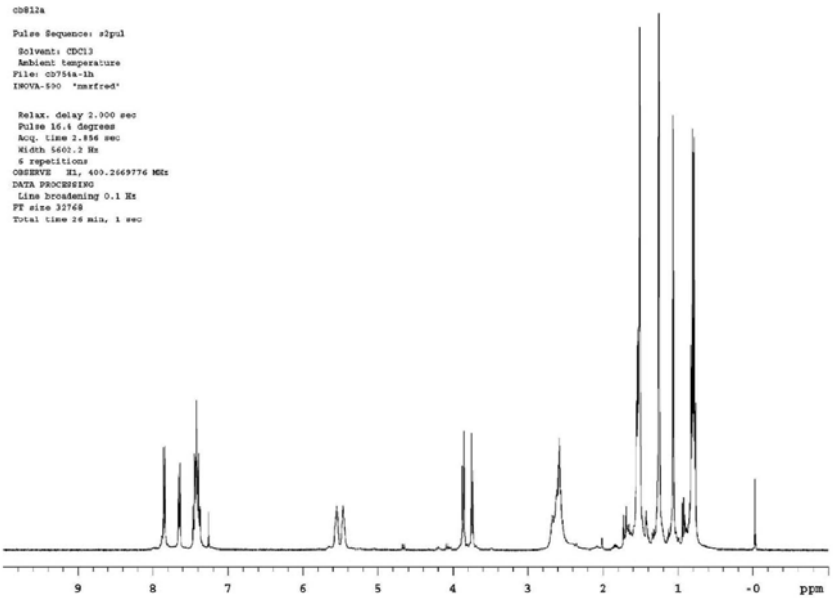
Procedure for the Formation of [Rh(cod)(AP-I)$_2$]OTf complex

(3a*R*,8a*R*)-6-(Benzo[b]thiophen-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (AP-I) (700 mg, 1.7 mmol, 210 mol%) and Rh(cod)$_2$OTf (375 mg, 0.8 mmol, 100 mol%) were dissolved in DCM (0.1 M) and stirred for 6 h at 25 ^{o}C. The solvent was removed under reduced pressure and the residue was triturated with dry degassed hexanes for 10 h with vigorous stirring. The resulting mixture was filtered, and the solid was dried under vacuum to give the product as a yellow powder (775 mg, 82% yield).

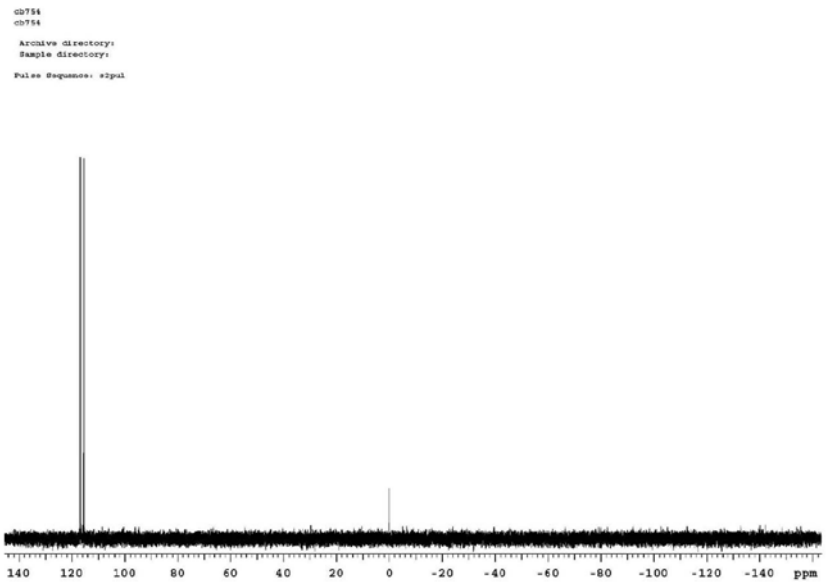
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.46-7.36 (m, 6H), 5.55 (bs, 2H), 5.47 (bs, 2H), 3.86 (d, *J* = 9.2 Hz, 2H), 3.74 (d, *J* = 9.2 Hz, 2H), 2.70-2.50 (m, 8H), 1.51 (m, 14H), 1.25 (m, 12H), 1.06 (s, 6H), 0.79 (q, *J* = 8.2 Hz,

12H). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 116.2 (d, $J_{P\text{-}Rh}$ = 220.0 Hz). MP: 142-146 ^{o}C (dec).

^{1}H NMR



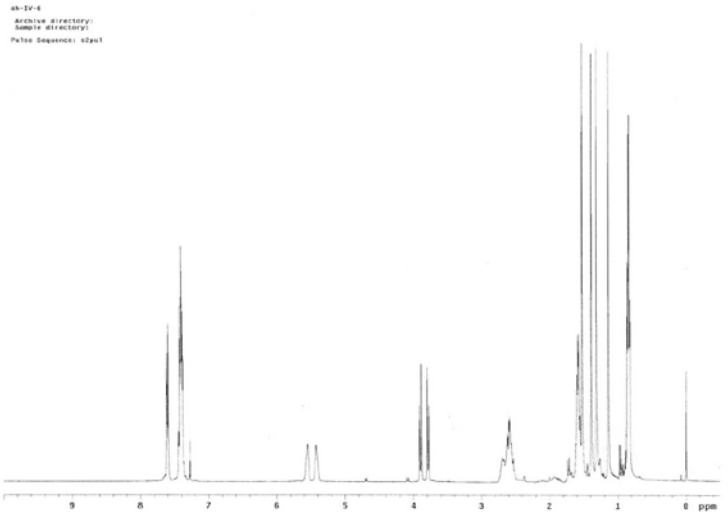
^{31}P NMR



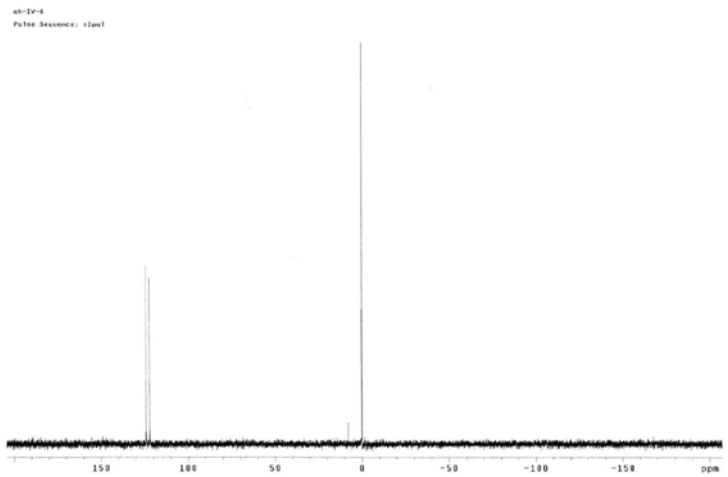
[Rh(cod)(AP-IV)$_2$]OTf

^{1}H NMR (400 MHz, CDCl3): δ 7.61-7.59 (m, 4H), 7.44-7.36 (m, 10H), 5.55 (bs, 2H), 5.42 (bs, 2H), 3.89 (d, *J* = 9.4Hz, 2H), 3.78 (d, *J* = 9.4Hz, 2H), 2.69-2.52 (m, 8H), 1.62 (m, 8H), 1.52 (s, 6H), 1.39 (s, 6H), 1.31 (s, 6H), 1.14 (s, 6H), 0.85 (t, *J* = 7.4Hz, 6H), 0.84 (t, *J* = 7.0 Hz, 6H). ^{31}P NMR (121.5 MHz, CDCl3): δ 123.1 (d, $J_{P\text{-}Rh}$ = 219.7 Hz). MP: 137-139 ^{o}C.

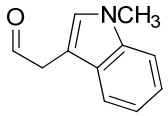
^{1}H NMR



^{31}P NMR



2-(1-methyl-1H-indol-3-yl)acetaldehyde

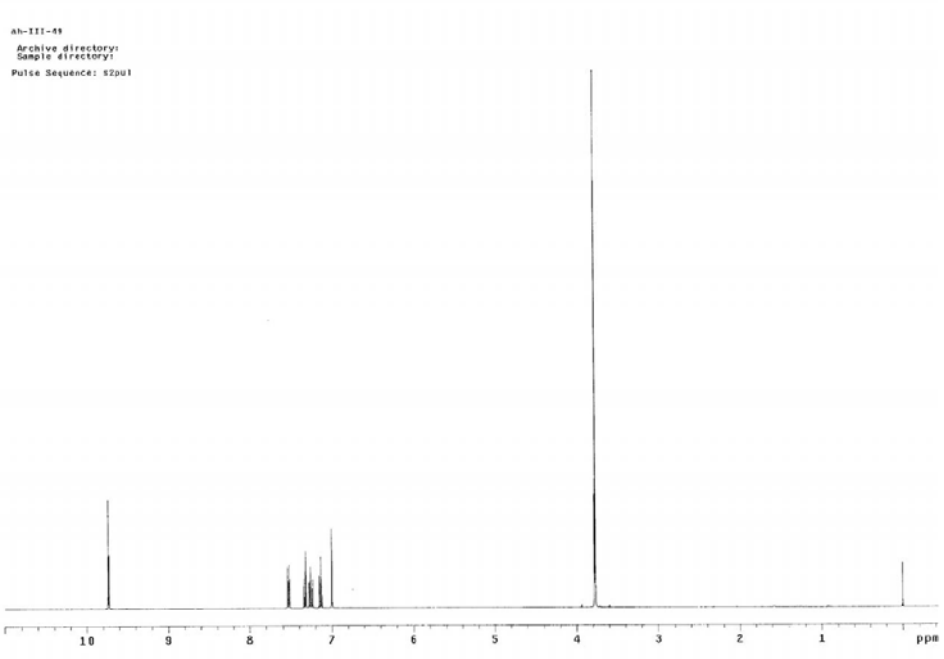


2.7f

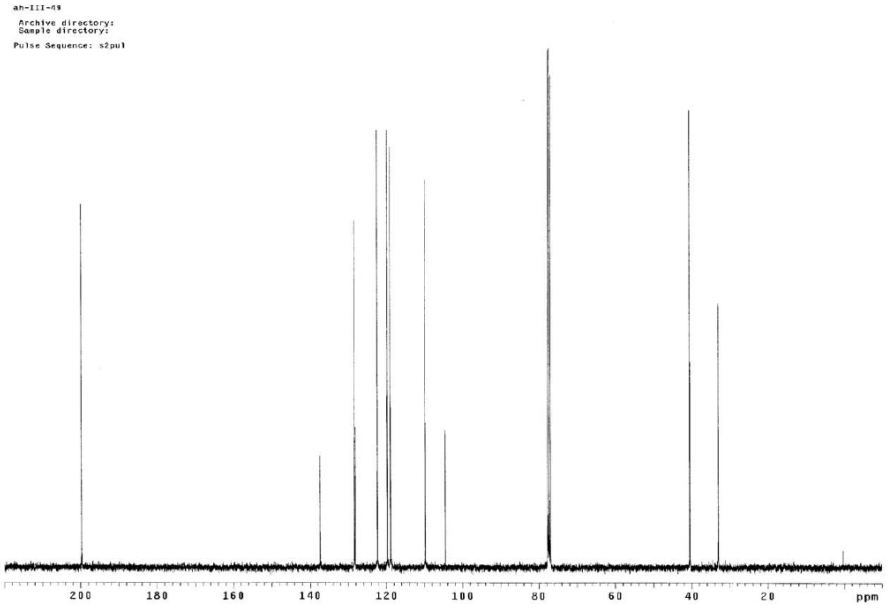
Neat DIBAL (3.4 mL, 19 mmol, 120 mol%) was added dropwise using a syringe pump to a solution of methyl N-methylindole-3-acetate (3.24 g, 16 mmol, 100 mol%) in DCM (0.08 M) at -78 °C over 30 minutes. The solution was allowed to stirr at -78 °C for 1 hour, at which point a cold (5 ^{o}C) saturated aqueous solution tartaric acid (200 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (200 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered and the resulting solution was subjected to rotary evaporation under reduced pressure to provide an oily residue, which upon purification by flash chromatography (SiO_2, 10% EtOAc/ Hexanes) followed by Kügelrohr distillation (180 °C/ 0.5 mmHg) provides the title compound in 72% yield as a pale green oil (2.0 g, 11.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 2.5 Hz, 1H), 7.52 (ddd, *J* = 7.8, 1.0, 1.0 Hz, 1H), 7.32 (ddd, *J* = 8.2, 1.0, 0.8 Hz, 1H), 7.26 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 6.99 (s, 1H), 3.78 (dd, *J* = 2.5, 0.8 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 137.3, 128.3, 122.3, 119.7(2C), 118.8, 109.7, 104.6, 40.5, 33.0. HRMS calcd for $C_{11}H_{12}NO$ (M+1): 174.0919, Found: 174.0922. FTIR (neat): 3054, 2934, 2822, 2719, 1721, 1616, 1550, 1474, 1425, 1373, 1350, 1330, 1251, 1156, 1013, 925 cm^{-1}.

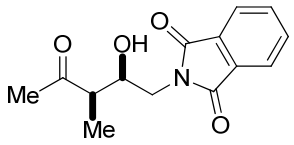
^{1}H NMR



^{13}C NMR



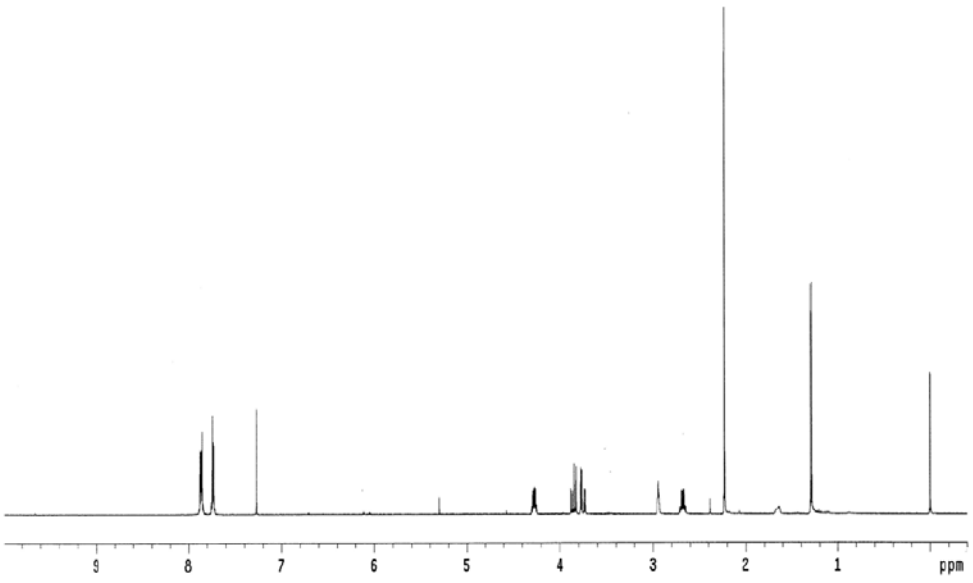
2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxopentyl)isoindoline-1,3-dione



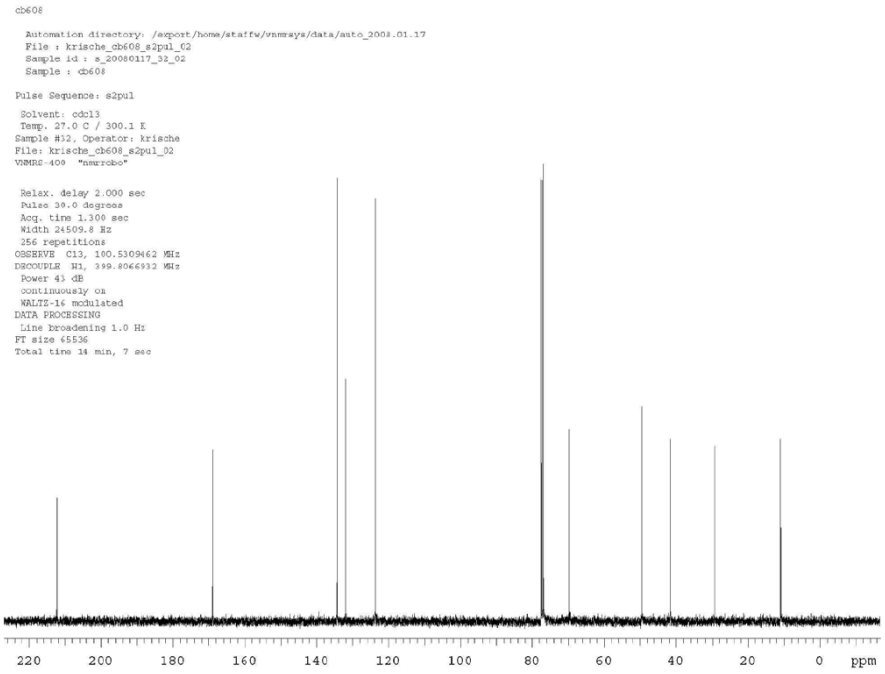
2.8a

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.84 (m, 2H), 7.74-7.72 (m, 2H), 4.30-4.25 (m, 1H), 3.85 (dd, *J* = 14.2, 7.4 Hz, 1H), 3.75 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.95-2.93 (m, 1H), 2.68 (dq, *J* = 4.2, 7.2 Hz, 1H), 2.23 (s, 3H), 1.29 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4, 169.0, 134.4, 132.1, 123.7, 69.9, 49.4, 41.7, 29.2, 10.9. HRMS Calcd for $C_{14}H_{15}NO_4$ (M+1): 261.1001, Found: 261.1004. FTIR (neat): 3435, 3053, 2978, 2935, 2872, 2306, 1640, 1446, 1383, 1351, 1266, 1114, 1076, 896, 743 cm^{-1}. Mp: 140-141 ^{o}C. HPLC: (Chiralpak AD-H column, 10% *i*-PrOH/ hexanes, 1 mL/ min, 254 nm), t_{major} = 30.5 min, t_{minor} = 34.7 min; ee = 96%. $[\alpha]_D^{25}$ +0.6, c = 1.6 in DCM

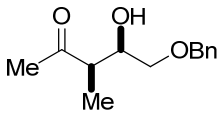
^{1}H NMR



^{13}C NMR



(3*R*,4*R*)-5-(benzyloxy)-4-hydroxy-3-methylpentan-2-one

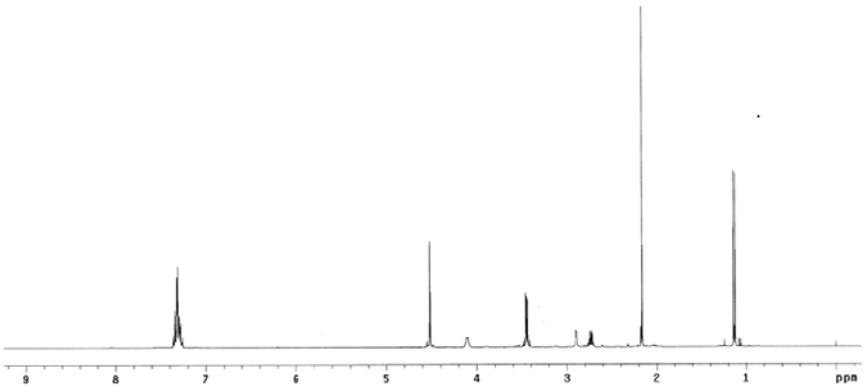


2.8b

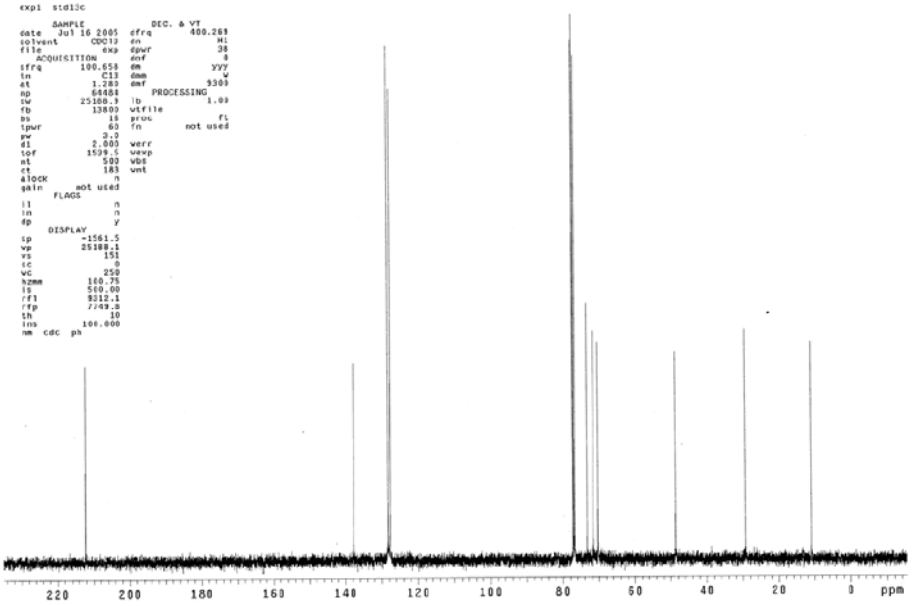
^{1}H NMR (400 MHz, $CDCl_3$): 7.26-7.36 (m, 5H), 4.51 (s, 2H), 4.09-4.10 (m, 1H), 3.41-3.53 (m, 2H), 2.90 (d, J = 2.7 Hz, 1H), 2.61-2.77 (dq, J = 7.2, 5.1 Hz, 1H), 2.16 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 212.2, 137.7, 128.3, 127.7, 127.6, 73.3, 71.6, 70.2, 48.6, 29.2, 11.0. HRMS Calcd for $C_{13}H_{18}O_3$ (M+1): 223.1334, Found: 223.1330. FTIR (neat): 3439, 3031, 2920, 2867, 1704, 1455, 1360, 1252, 1207, 1181, 1094, 1028, 957, 916, 739, 699 cm^{-1}. HPLC: (Chiralpak AS-H column, 10% *i*-PrOH/

hexanes, 0.8 mL/ min, 254 nm), t_{major} = 9.7 min, t_{minor} = 11.3 min; ee = 91%. $[\alpha]_D^{25}$ -5°, c = 1.0 in DCM

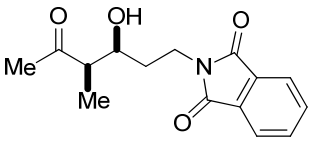
^{1}H NMR



^{13}C NMR



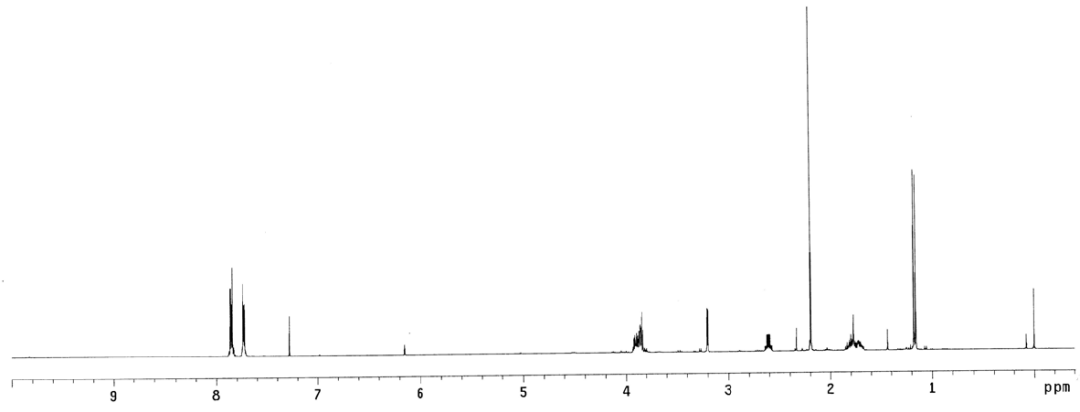
2-((3*S*,4*R*)-3-hydroxy-4-methyl-5-oxohexyl)isoindoline-1,3-dione



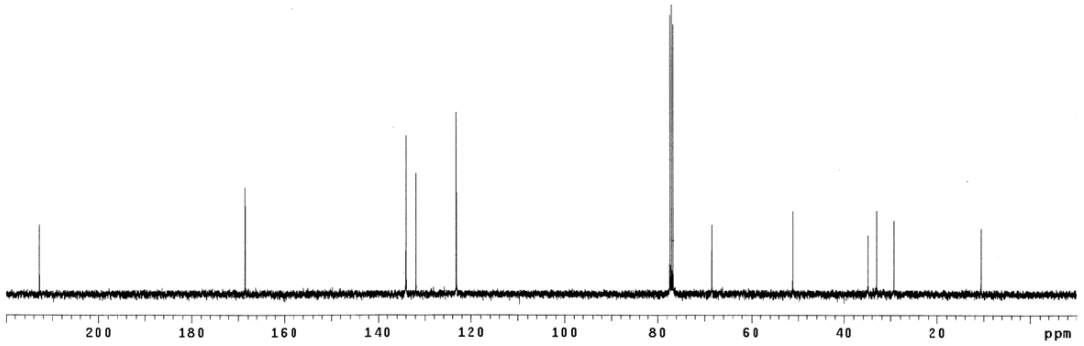
2.8c

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.75-7.71 (m, 2H), 3.93-3.77 (m, 3H), 3.20 (d, *J* = 3.8 Hz, 1H), 2.61 (dq, *J* = 3.8, 7.2 Hz, 1H), 2.19 (s, 3H), 1.85-1.67 (m, 2H), 1.17 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.8, 168.6, 134.0, 131.9, 123.2, 68.4, 51.1, 34.8, 33.0, 29.3, 10.5. HRMS: Calcd [M] for $C_{15}H_{17}NO_4$: 275.1158; Found: 275.1156. FTIR (film): 3469, 3054, 2986, 2305, 2254, 1771, 1710, 1468, 1397, 1372, 1265, 1177, 951, 910, 741 cm^{-1}. HPLC: (Chiralpak AD-H column, 5% *i*-PrOH/ hexanes, 1.0 mL/ min, 220 nm), t_{minor} = 57.2 min, t_{major} = 66.5 min; ee = 89%.

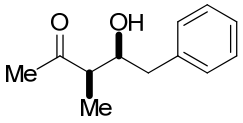
^{1}H NMR



^{13}C NMR



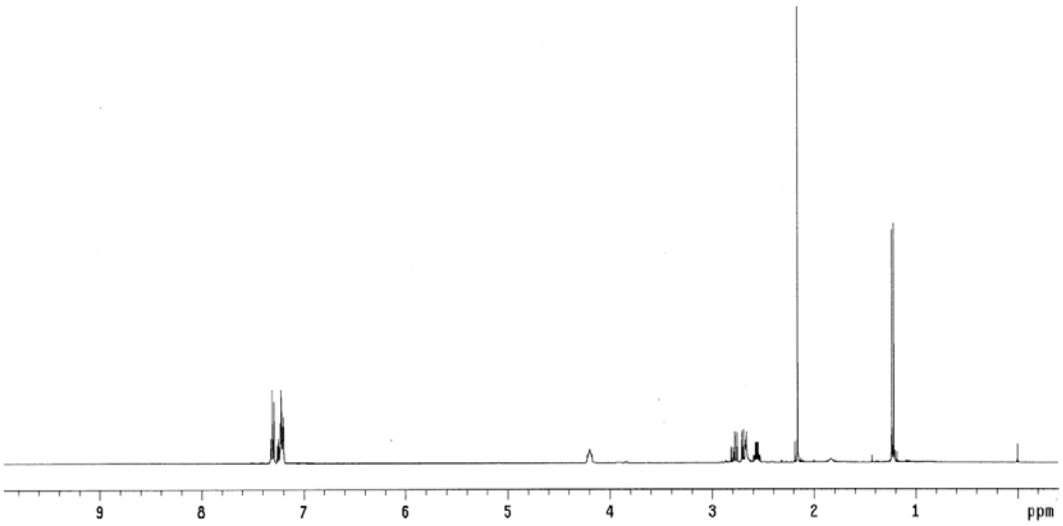
(3*R*,4*S*)-4-hydroxy-3-methyl-5-phenylpentan-2-one



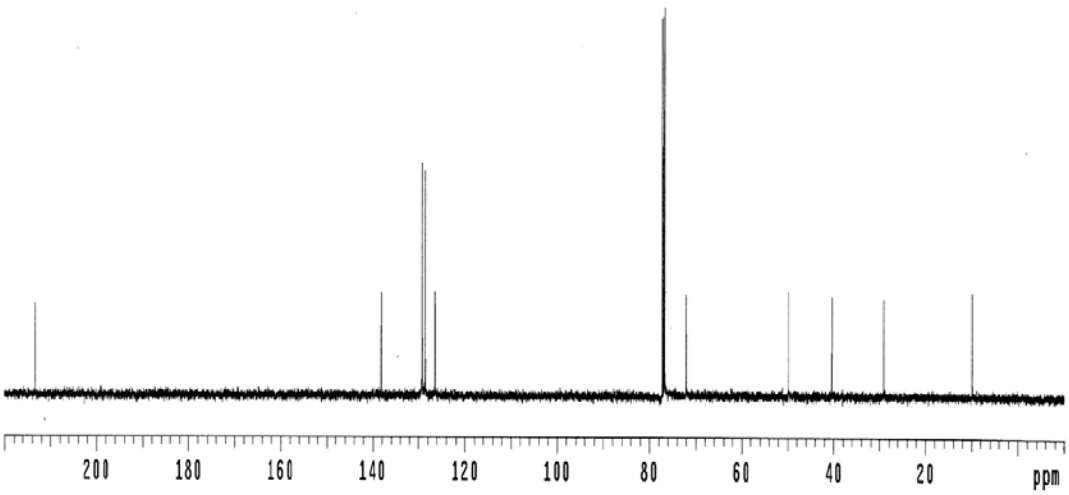
2.8d

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 7.2 Hz, 3H), 2.16 (s, 3H), 2.56 (dq, *J* = 3.4, 7.2 Hz, 1H), 2.67-2.68 (br, 1H), 2.69 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.79 (dd, *J* = 13.7, 7.9 Hz, 1H), 4.18-4.22 (m, 1H), 7.20-7.26 (m, 3H), 7.28-7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.4, 138.1, 129.2, 128.5, 126.5, 72.0, 49.9, 40.3, 29.1, 9.9. HRMS Calcd for $C_{12}H_{16}O_2$ (M+1): 193.1229, Found: 193.1227. FTIR (neat): 3501, 3054, 2985, 2685, 2306, 1701, 1603, 1496, 1455, 1358, 1266, 1171, 1031, 909, 896, 734 cm^{-1}. HPLC: (Chiralpak OJ-H column, 7% *i*-PrOH/ hexanes, 0.8 mL/ min, 254 nm), t_{minor} = 15.0 min, t_{major} = 16.7 min; ee = 90%.

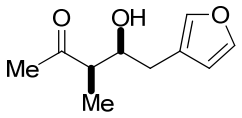
^{1}H NMR



^{13}C NMR



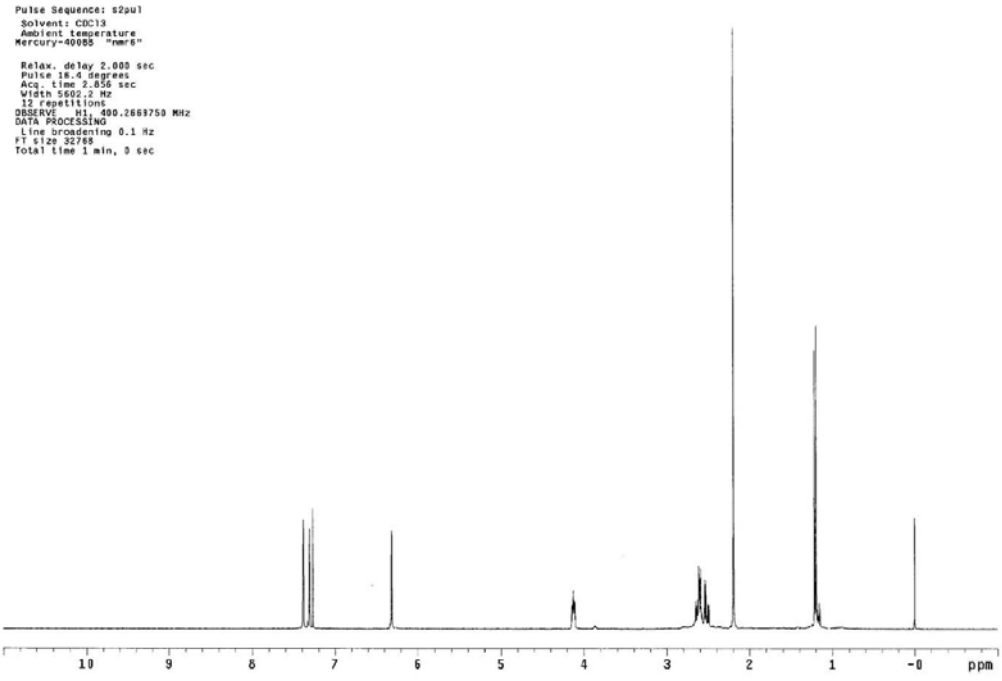
(3*R*,4*S*)-5-(furan-3-yl)-4-hydroxy-3-methylpentan-2-one



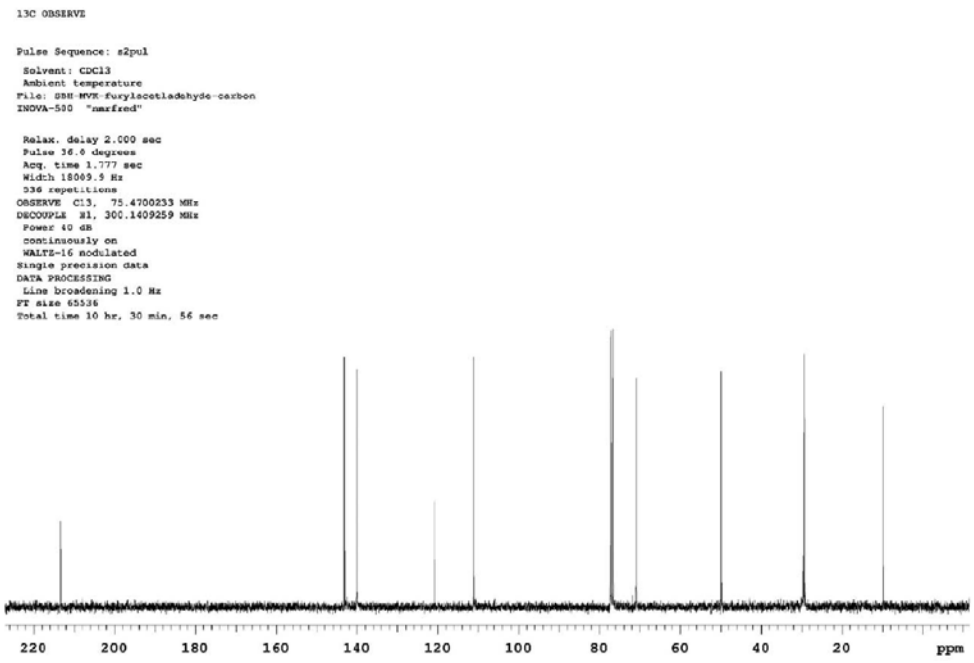
2.8e

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.31 (s, 1H), 6.32 (s, 1H), 4.15-4.11 (m, 1H), 2.65-2.50 (m, 4H), 2.19 (s, 3H), 1.61 (dd, *J* = 7.6 Hz, 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.4, 143.1, 140.0, 120.9, 111.1, 70.9, 49.9, 29.5, 29.1, 9.8. HRMS calcd for $C_{10}H_{15}O_3$ (M+1): 183.1021, Found: 183.1025. FTIR (neat): 3445, 2922, 1699, 1457, 1360, 1157, 1067, 1024, 874, 787, 734, 601 cm^{-1}. HPLC: (Chiralpak AD-H column, 2% *i*-PrOH/ hexanes, 1 mL/ min, 230 nm), t_{major} = 12.3 min, t_{minor} = 13.9 min; ee = 87%.

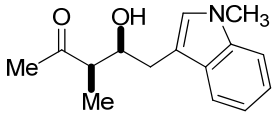
^{1}H NMR



^{13}C NMR



(3*R*,4*S*)-4-hydroxy-3-methyl-5-(1-methyl-1H-indol-3-yl)pentan-2-one

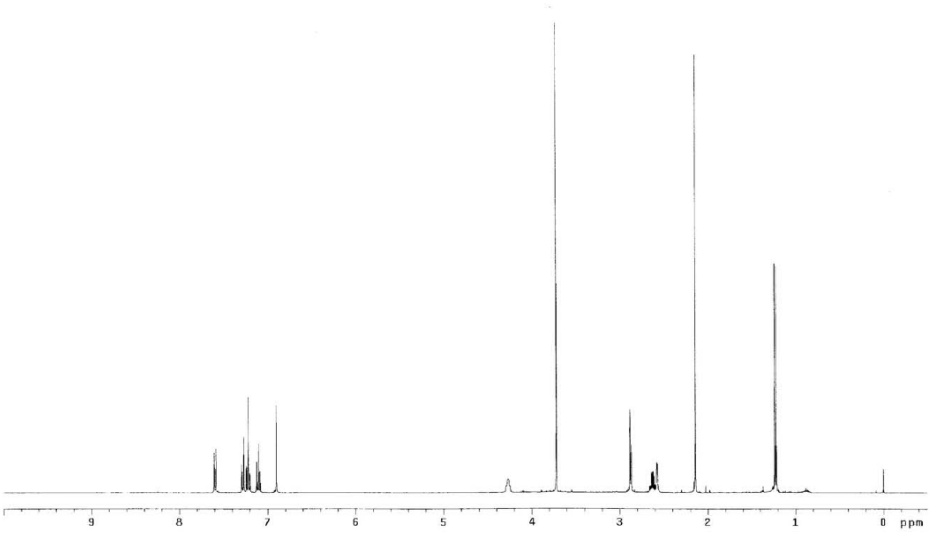


2.8f

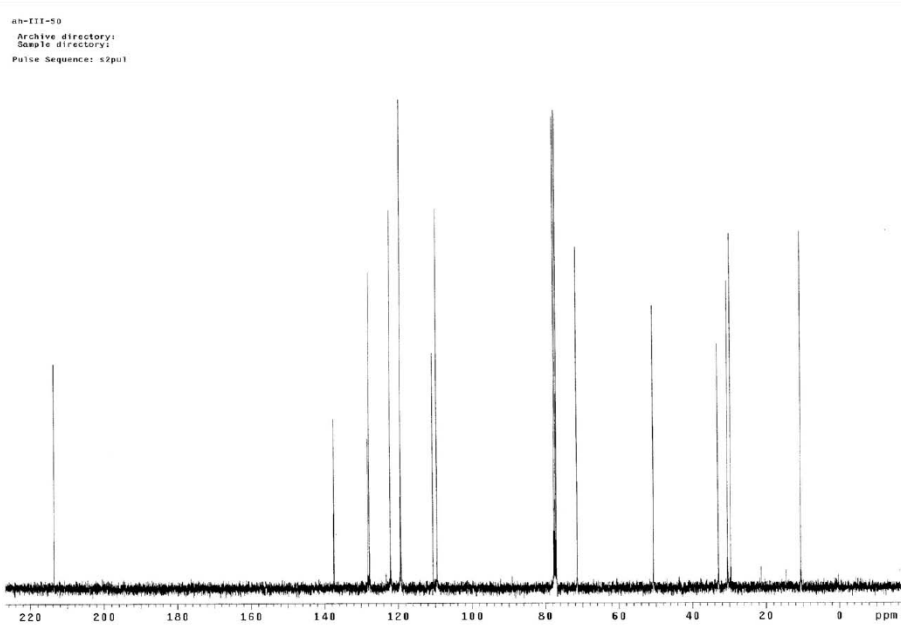
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (ddd, *J* = 7.9, 1.9, 1.2 Hz, 1H), 7.28 (ddd, *J* = 8.2, 1.8, 1.0 Hz, 1H), 7.22 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.10 (ddd, *J* = 7.9, 6.9, 1.2 Hz, 1H), 6.90 (s, 1H), 4.26 (m, 1H), 3.72 (s, 3H), 2.88 (s, 1H), 2.86 (dd, J = 1.6, 0.6, 1H), 2.62 (qd, *J* = 7.3, 4.0, 1H), 2.57 (m, 1H), 2.14 (s, 3H), 1.23 (d, *J* = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.5, 137.4, 128.1, 127.7, 122.0, 119.2(2C), 110.6, 109.6, 71.4, 50.6, 32.9, 30.4, 29.5, 10.5. HRMS calcd for $C_{15}H_{20}NO_2$ (M+1): 246.1494, Found: 246.1491. FTIR

(neat): 3446, 3053, 2935, 1704, 1615, 1472, 1425, 1375, 1357, 1328, 1250, 1173, 1155, 1126, 1091, 1070, 1032, 1012, 981 cm^{-1}. HPLC: (Chiralpak OD-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 254 nm), t_{minor} = 67.2 min, t_{major} = 71.4 min; ee = 86%.

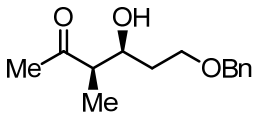
^{1}H NMR



^{13}C NMR



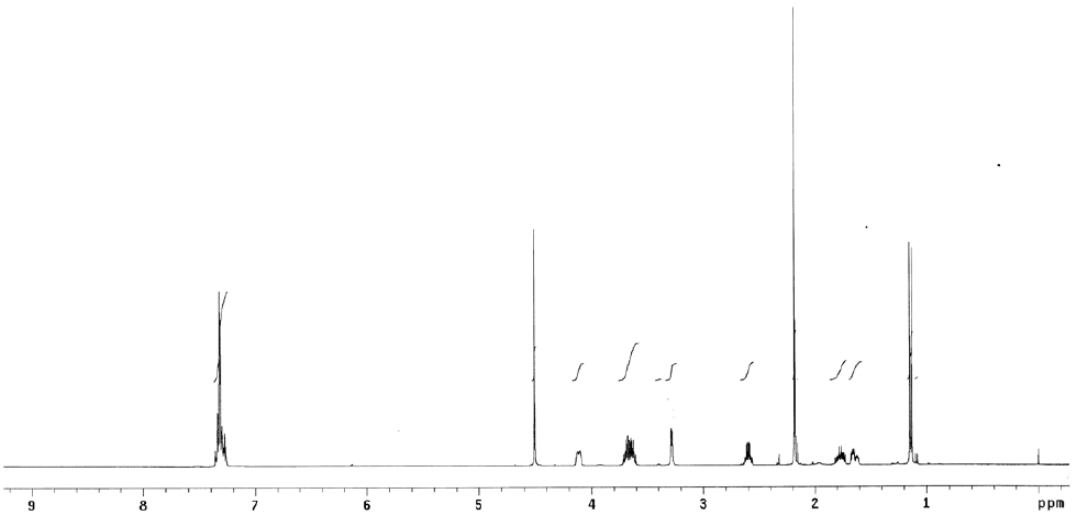
(3*R*,4*S*)-6-(benzyloxy)-4-hydroxy-3-methylhexan-2-one



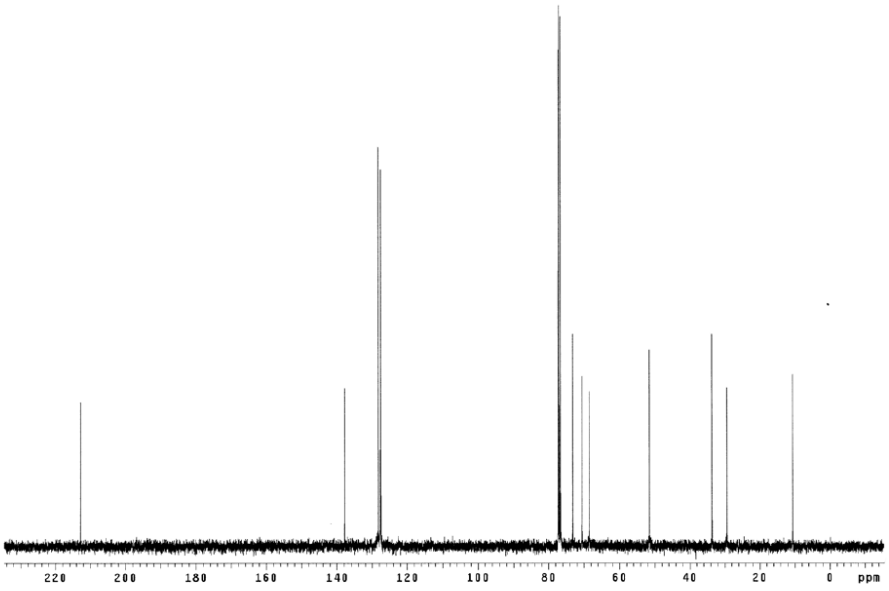
2.8g

^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.26 (m, 5H), 4.51 (s, 2H), 4.13-4.10 (m, 1H), 3.71-3.60 (m, 2H), 3.28 (d, *J* = 2.1, 1 H), 2.66-2.57 (m, 1H), 2.18 (s, 3H), 1.82-1.73 (m, 1H), 1.68-1.61 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 212.8, 137.8, 128.3, 127.6, 127.5, 73.2, 70.5, 68.5, 51.5, 33.6, 29.3, 10.6. HRMS Calcd [M+1] for $C_{14}H_{20}O_3$: 237.1491, Found: 237.1496. FTIR (film): 3433, 3031, 2924, 2868, 1701, 1455, 1362, 1207, 1181, 1098, 1028, 737, 699 cm^{-1}. HPLC: (Chiralpak AS-H column, 10% *i*-PrOH/ hexanes, 0.8 mL/ min, 254 nm), t_{major} = 9.6 min, t_{minor} = 13.8 min; ee = 88%.

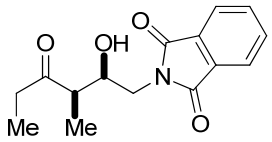
^{1}H NMR



^{13}C NMR



2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxohexyl)isoindoline-1,3-dione

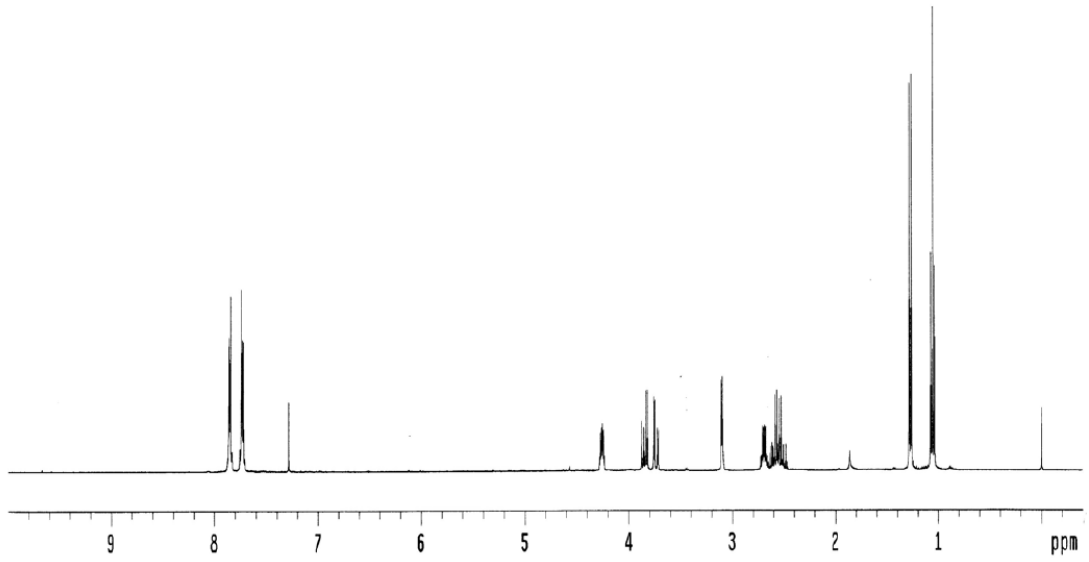


2.9a

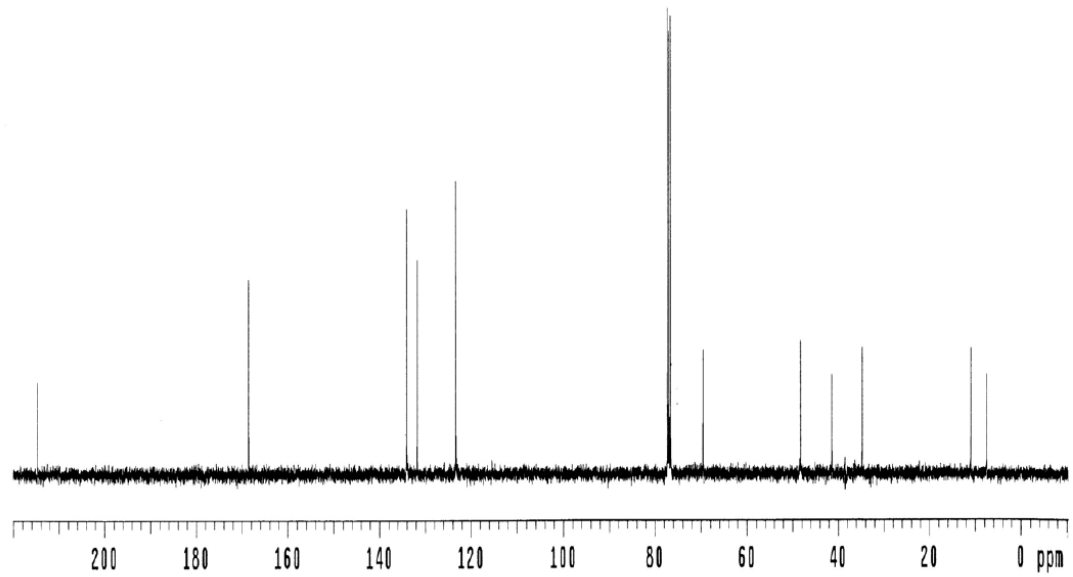
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.83 (m, 2H), 7.76-7.71 (m, 2H), 4.28-4.23 (m, 1H), 3.85 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.73 (dd, *J* = 14.2, 4.6 Hz, 1H), 3.10 (d, *J* = 3.8 Hz, 1H), 2.69 (dq, *J* = 4.3, 7.2 Hz, 1H), 2.60 (dq, *J* = 18.1, 7.2 Hz, 1H), 2.51 (dq, *J* = 18.1, 7.2 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 168.6, 134.0, 131.8, 123.3, 69.6, 48.2, 41.3, 34.7, 10.9, 7.4. HRMS Calcd for $C_{15}H_{17}NO_4$ (M+1): 275.1158, Found: 275.1158. FTIR (neat): 3454, 3054, 2986, 2305,

2254, 1773, 1714, 1642, 1422, 1397, 1265, 909, 748 cm^{-1}. HPLC: (Chiralpak AD-H column, 4% *i*-PrOH/ hexanes, 1.0 mL/ min, 254 nm), t_{minor} = 91.4 min, t_{major} = 97.1 min; ee = 96%. $[\alpha]_D^{25}$ +1.4, c = 1.4 in DCM

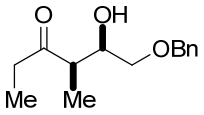
^{1}H NMR



^{13}C NMR



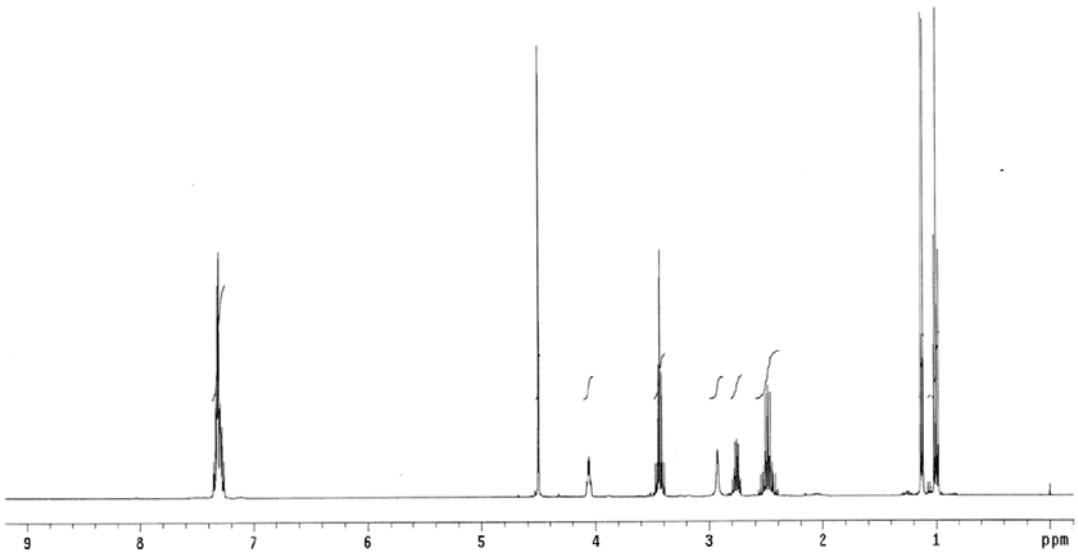
(4*R*,5*R*)-6-(benzyloxy)-5-hydroxy-4-methylhexan-3-one



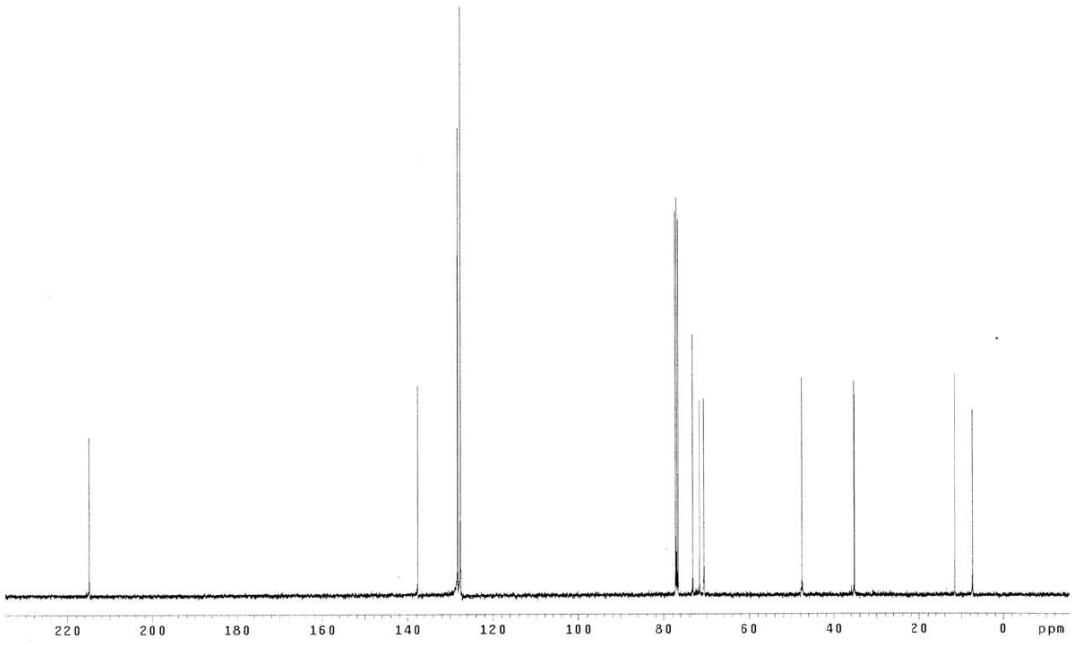
2.9b

^{1}H NMR (400 MHz, $CDCl_3$): 7.26-7.36 (m, 5H), 4.50 (s, 2H), 4.05 (q, *J* = 5.4, 1H), 3.40-3.47 (m, 2H), 2.93 (s, 1H), 2.73-2.80 (dq, *J* = 5.1, 7.2 Hz, 1H), 2.40-2.57 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 214.9, 137.7, 128.3, 127.7, 73.3, 71.6, 70.5, 47.6, 35.2, 11.5, 7.4. HRMS Calcd for $C_{14}H_{20}O_3$ (M+1): 237.1491, Found: 237.1488. FTIR (neat): 3502, 3064, 3031, 2977, 2938, 1705, 1497, 1455, 1410, 1376, 1250, 1208, 1099, 1028, 976, 915, 738, 699 cm^{-1}. HPLC: (Chiralpak OD-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 254 nm), t_{minor} = 20.8 min, t_{major} = 26.4 min; ee = 88%.

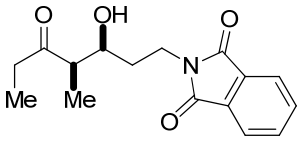
^{1}H NMR



^{13}C NMR



2-((3*S*,4*R*)-3-hydroxy-4-methyl-5-oxoheptyl)isoindoline-1,3-dione

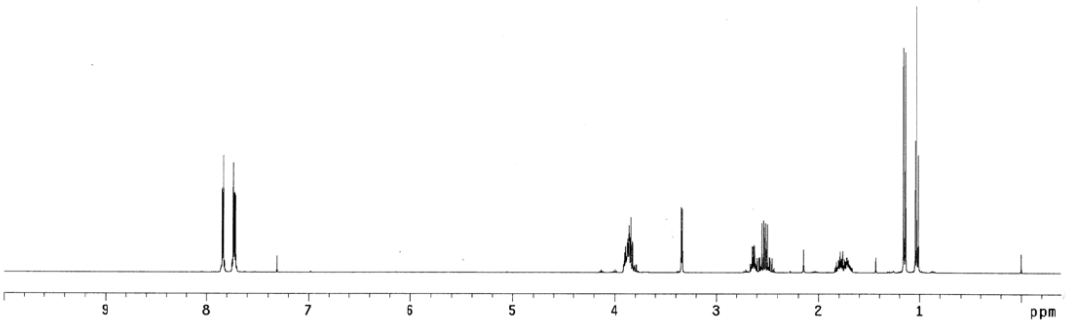


2.9c

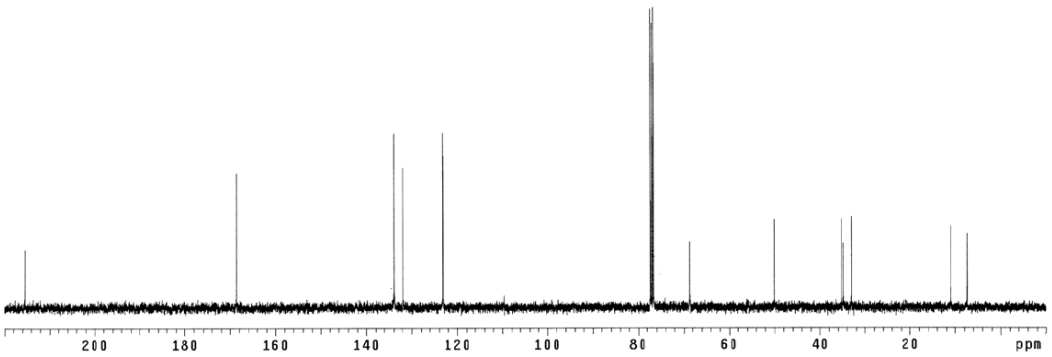
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.81 (m, 2H), 7.75-7.71 (m, 2H), 3.91-3.71 (m, 3H), 3.34 (d, *J* = 4.1 Hz, 1H), 2.64 (dq, *J* = 4.4, 7.2 Hz, 1H), 2.57 (dq, *J* = 18.1, 7.3 Hz, 1H), 2.49 (dq, *J* = 18.1, 7.2 Hz, 1H), 1.84-1.67 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 138.6, 133.9, 131.9, 123.2, 68.6, 50.1, 35.3, 34.8, 33.0, 11.0, 7.4. HRMS: Calcd [M] for $C_{16}H_{19}NO_4$: 289.1314; Found:

289.1316. FTIR (film): 3466, 3054, 2985, 2305, 2254, 1771, 1710, 1468, 1397, 1265, 952, 911, 741 cm^{-1}. HPLC: (Chiralpak AS-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 220 nm), t_{minor} = 78.5 min, t_{major} = 91.8 min; ee = 92%. $[\alpha]_D^{25}$ -5.0°, c = 1.0 in DCM

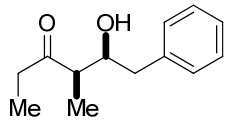
^{1}H NMR



^{13}C NMR



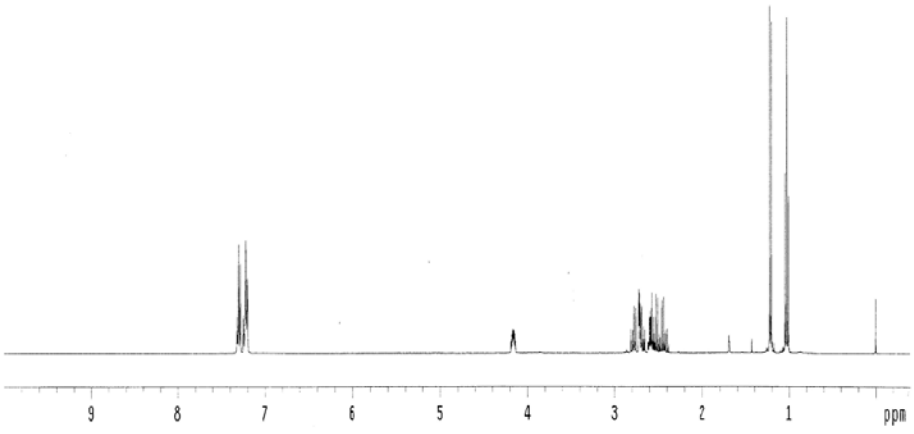
(4*R*,5*S*)-5-hydroxy-4-methyl-6-phenylhexan-3-one



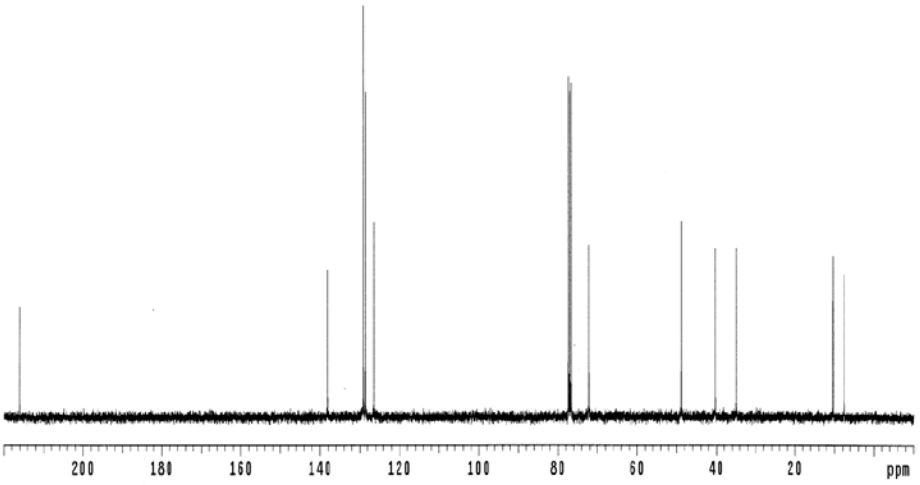
2.9d

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.20 (m, 5H), 4.19-4.14 (m, 1H), 2.79 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.72-2.72 (m, 1H), 2.68 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.59 (dq, *J* = 3.4, 7.2 Hz, 1H), 2.52 (dq, *J* = 18.1, 7.3 Hz, 1H), 2.43 (dq, *J* = 18.1, 7.3 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 216.1, 138.2, 129.1, 128.4, 126.4, 72.2, 48.8, 40.3, 35.0, 10.3, 7.5. HRMS Calcd for $C_{13}H_{18}O_2$ (M+1): 207.1385, Found: 207.1385. FTIR (neat): 3943, 3512, 3054, 2984, 2941, 2685, 2305, 1698, 1604, 1496, 1455, 1421, 1379, 1265, 1110, 1030, 976, 896, 737 cm^{-1}. HPLC: (Chiralpak OD-H column, 2% *i*-PrOH/ hexanes, 1.0 mL/ min, 254 nm), t_{minor} = 12.6 min, t_{major} = 14.6 min; ee = 90%.

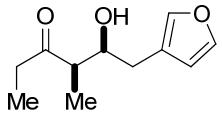
^{1}H NMR



^{13}C NMR



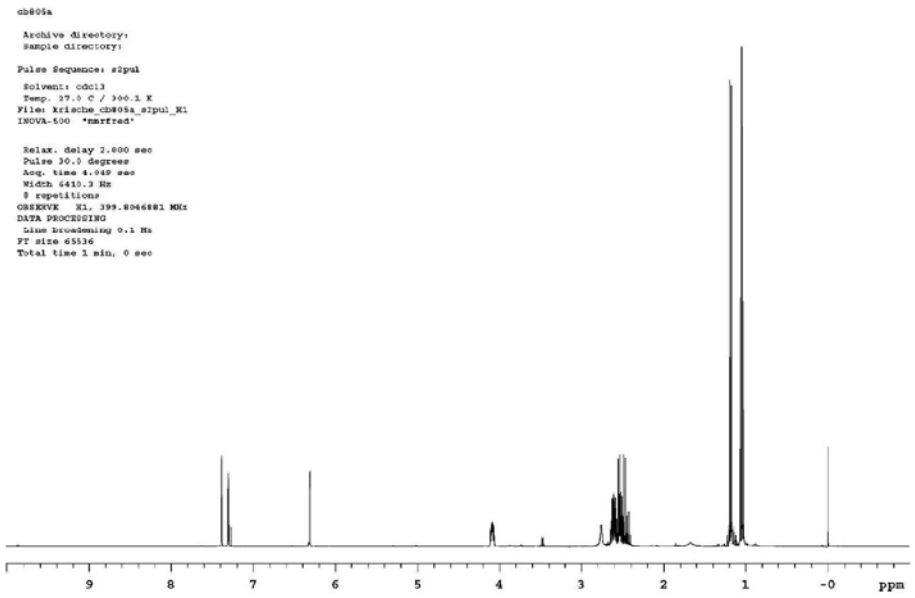
(4*R*,5*S*)-6-(furan-3-yl)-5-hydroxy-4-methylhexan-3-one



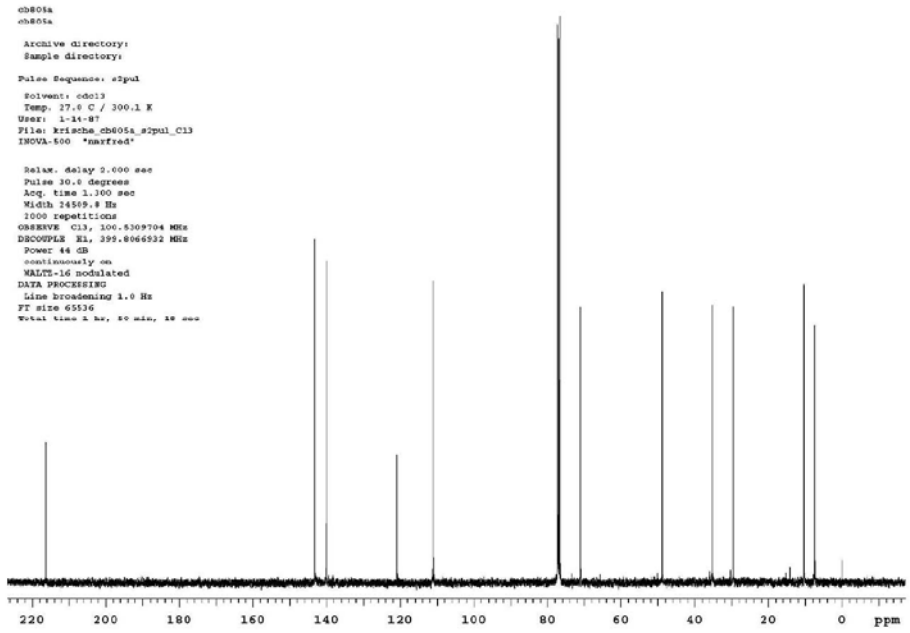
2.9e

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–73.7 (m, 1H), 7.31–7.29 (m, 1H), 6.32–6.30 (m, 1H), 4.11–4.06 (m, 1H), 2.88–2.73 (bs, 1H), 2.66–2.42 (m, 5H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.2, 143.1, 140.1, 121.0, 111.1, 71.1, 48.8, 35.2, 29.5, 10.3, 7.6. HRMS calcd for $C_{11}H_{17}O_3$ (M+1): 197.1178, Found: 197.1180. FTIR (neat): 3441, 2977, 2938, 1709, 1502, 1461, 1378, 1157, 1109, 1502, 1461, 1378, 1157, 1109, 1024, 976, 874, 786 cm^{-1}. HPLC: (Chiralpak AD-H column, 5% *i*-PrOH/ hexanes, 1 mL/ min, 230 nm), t_{minor} = 11.6 min, t_{major} = 13.6 min; ee = 88%.

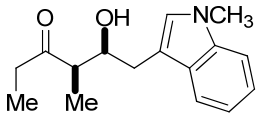
^{1}H NMR



^{13}C NMR



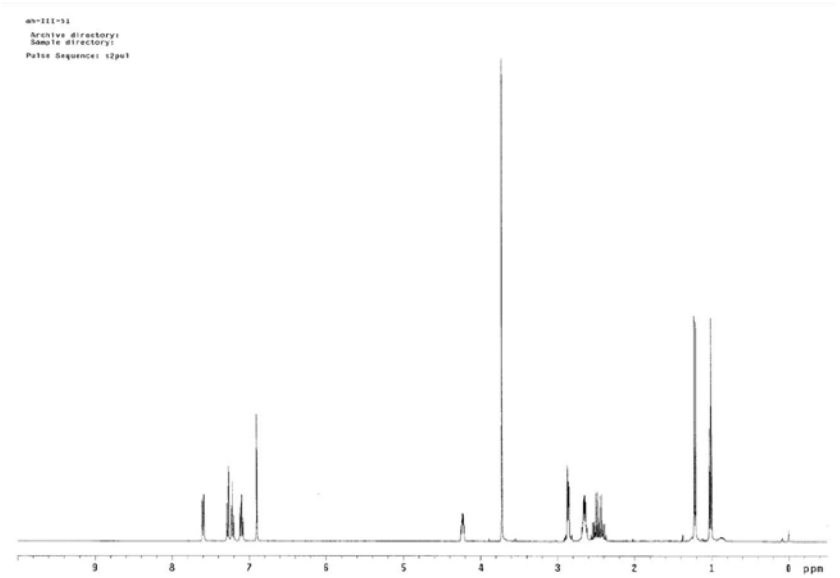
(4*R*,5*S*)-5-hydroxy-4-methyl-6-(1-methyl-1H-indol-3-yl)hexan-3-one



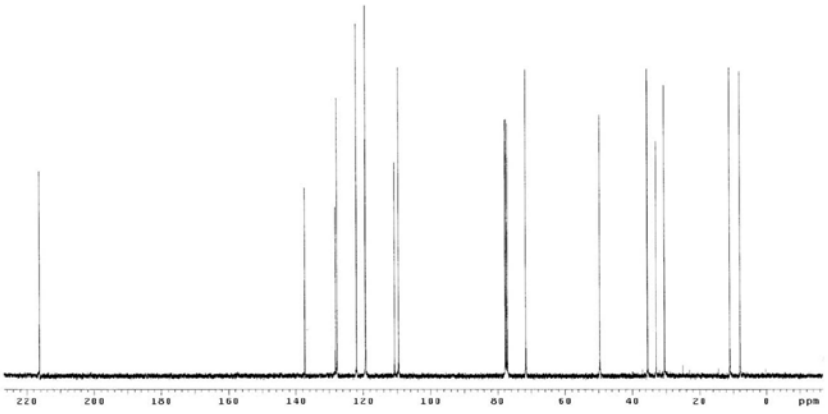
2.9f

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.28 (m, 1H), 7.22 (m, 1H), 7.10 (m, 1H), 6.90 (s, 1H), 4.24 (ddd, *J* = 10.4, 6.3, 4.2 Hz, 1H), 3.72 (s, 3H), 2.88 (s, 1H), 2.86 (d, *J* = 3.2 Hz, 1H), 2.65 (m, 2H), 2.47 (m, 2H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.3, 137.4, 128.2, 127.7, 122.0, 119.3, 119.2, 110.7, 109.6, 71.7, 49.6, 35.4, 32.9, 30.4, 11.0, 7.8. HRMS calcd for $C_{16}H_{22}NO_2$ (M+1): 260.1651, Found: 260.1649. FTIR (neat): 3474, 3054, 2975, 2036, 1704, 1615, 1552, 1473, 1425, 1376, 1328, 1250, 1155, 1132, 1061, 1012, 974, 741 cm^{-1}. HPLC: (Chiralpak OJ-H column, 10% *i*-PrOH/ hexanes, 1 mL/ min, 254 nm), t_{minor} = 17.5 min, t_{major} = 20.6 min; ee = 90%

^{1}H NMR



^{13}C NMR

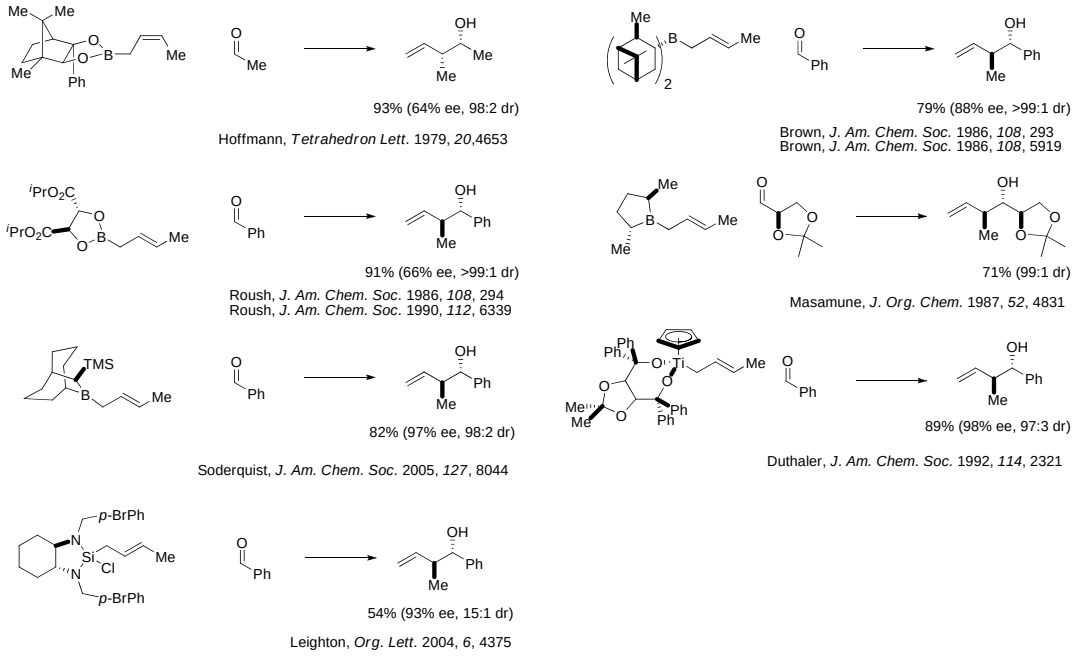


Chapter 3 Enantioselecive Iridium-Catalyzed Carbonyl Allylation *via* Transfer Hydrogenation

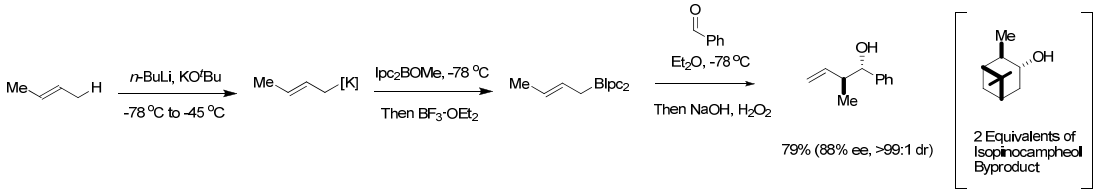
3.1 ENANTIOSELECIVE IRIDIUM-CATALYZED CARBONYL CROTYLATION

3.1.1 Background

Carbonyl crotylation is the one of the most important reactions for the generation of polypropionate units of natural products.[1] Most enantioselective crotylation methods employ chirally modified, preformed metal reagents. A variety of such reagents have been developed over the past few decades, including Boron-crotyl reagents (Hoffmann[2a], Brown[2b,c], Roush[2d,e], Masamune[2f], and Soderquist[2g]), Ti-crotyl reagents (Duthaler[2h,i]) and



Scheme 3.1 Representative examples of chirally modified crotyl metal reagents for use in enantioselective carbonyl crotylation.

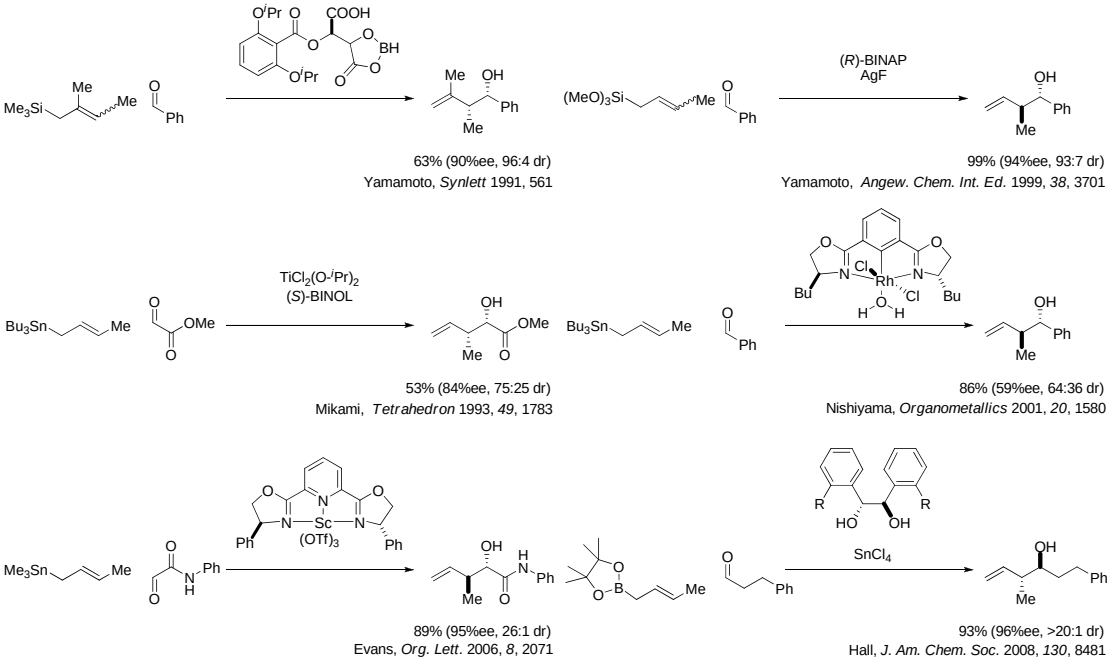


Scheme 3.2 Multi-step preparation of Brown's crotylating reagent and reaction with aldehyde.

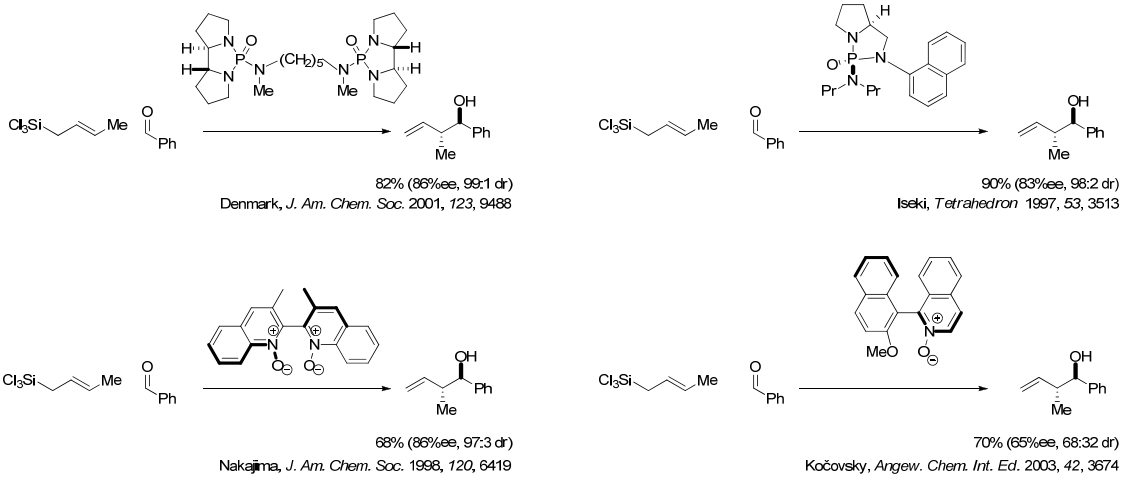
Si-crotyl reagents (Panek[2j,k] and Leighton[2l]) (Scheme 3.1). However, most chirally modified crotyl metal reagents generate stoichiometric byproducts and require multiple modified crotyl metal reagents generate stoichiometric byproducts and require multiple steps for preparation. For example, the commonly used Brown's crotylating reagent is prepared from potassiation of butane with Schlosser's base [3] and subsequent transmetalation to boron (Scheme 3.2). These manipulations require stoichiometric reagents such as *n*-BuLi, KO*t*Bu and Ipc_2BOMe and inevitably generate stoichiometric byproducts in the form of metal salts. Moreover, two equivalents of isopinocampheol are produced as one crotyl moiety is delivered, which must be separated from the product. Separation of these superstoichiometric quantities of secondary alcohol byproduct from the product, a secondary alcohol, may not be a trivial procedure.

There have been efforts to address these issues by developing catalytic protocols for carbonyl crotylation, which avoid the stoichiometric use of chirally modified crotyl metal reagents. Lewis acids (Yamamoto[4a-c], Mikami[4d], Nishiyama[4e], Evans[4f] and Hall[4g,h]) and bases (Denmark [5 a,b], Iseki[5c], Nakajima[5d] and Kočovsky[5e]) can be used for enantioselective crotylations. Additionally, a chiral diol (Schaus[6]) is reported as a catalyst

Lewis Acid



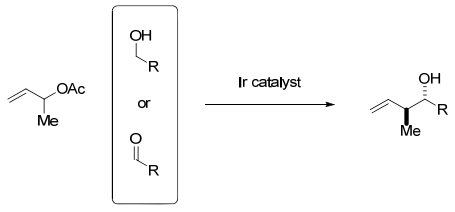
Lewis Base



Scheme 3.3 Representative examples of Lewis acid and base catalyzed asymmetric carbonyl crotylation.

for allylboration of ketones (Scheme 3.3). Alternate catalytic methods, including the enantioselective variants of the Nozaki-Hiyama reaction, are reported.[7,8] In this approach, reductive generation of crotylmetal reagents from the corresponding halides is used. Although these methods effectively produce the crotylation product, they remain dependent on preformed crotyl metal reagents, which generate stoichiometric amount of waste. For example, the protocol for allyl stannane production generates tin byproducts, and allyl trichlorosilanes used in the Denmark allylation produce stoichiometric amounts of hydrochloric acid upon hydrolysis. In the case of the catalytic variants of Nozaki-Hiyama-Kischi reactions, stoichiometric amounts of metallic reductants, such as $SnCl_2$, SmI_2, Et_2Zn, and Et_3B must be employed for catalytic turnover.

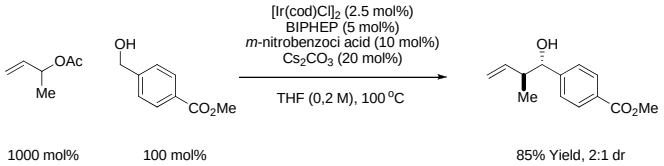
Based on recently developed iridium catalyzed enantioselective allylation reaction,[2] enantioselective carbonyl crotylations which employ α-methyl allyl acetate were sought (Scheme 3.4). This catalytic transformation does not employ any stoichiometric organometallic reagents and achieves highly enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level.



Scheme 3.4 Iridium catalyzed carbonyl crotylation.

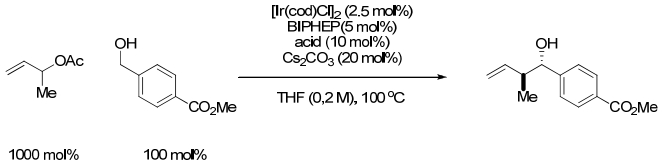
3.1.2 Reaction Optimization

The initial screen for the crotylation began with an attempt to couple α-methyl allyl acetate and alcohol under our first-generation catalytic system,[2] which employs an iridium complex generated *in situ* (Scheme 3.5).

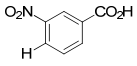
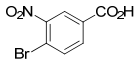
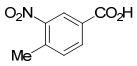
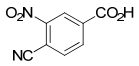
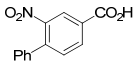
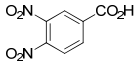
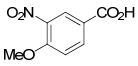
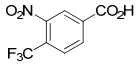
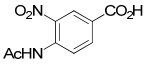
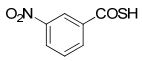
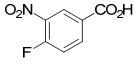
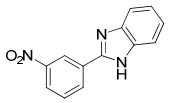
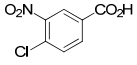
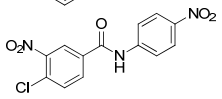


Scheme 3.5 Carbonyl crotylation with iridium complex generated *in situ*.

This reaction gave carbonyl crotylation product with complete branch regioselectivity in 85% yield. However, poor *anti*-diastereoselectivities (2:1 dr) were observed. The subsequent discovery that the active catalyst is an ortho-cyclometallated iridium *C*,*O*-benzoate[2] unveiled new opportunities to direct diastereoselectivity involving modification of the cyclometallating agent. Accordingly, a range of substituted benzoic acids were assayed to increase the diastereoselectivity (Table 3.1). This assay focused primarily on 4-substituted-3-nitrobenzoic acids, as substitution at the 2-, 5- and 6-positions substantially diminished the reactivity of the resulting catalytic complex. Among 4-substituted-3-nitrobenzoic acids, the 4-cyano-3-nitrobenzoic acid (Table 3.1, entry 9) and 3, 4-dinitrobenzoic acid (Table 3.1, entry 10) gave the highest diastereoselectivity with 3.0:1 and 3.5:1 respectively. Alternative cyclometallating agents were ineffective (Table 3.1, entry 12-14).



1000 mol% 100 mol%

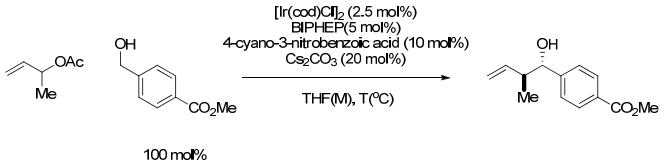
Entry	Acid	Yield (%)	dr	Entry	Acid	Yield (%)	dr
1[a]		85	2.0:1	8		80	2.4:1
2[a]		72	2.7:1	9		70	3.0:1
3		10	2.0:1	10		65	3.5:1
4[a]		68	2.2:1	11[a]		86	2.4:1
5		50	1.5:1	12		38	1.9:1
6[a]		78	2.3:1	13		5	1.2:1
7		93	2.6:1	14		7	1.9:1

[a] conducted by Dr. In Su Kim

Table 3.1 Assay of substituted benzoic acids.

Having these acids in hand, different loadings of α-methyl allyl acetate were tested (Table 3.2). Interestingly, a reduction in the loading of α-methyl allyl acetate from 1000 to 500 to 200 mol % was found to increase the level of *anti*-diastereoselection from 3.0:1 to 3.7:1 to 4.3:1, respectively (Table 3.2, entry 1, 2 and 3). Remarkably, at 200 mol % loadings of α-methyl allyl acetate, both diastereoselectivity and isolated yield were found to improve substantially with increasing concentration. At 0.2, 0.5, and 1.0 M

concentrations, *anti*-diastereoselectivities increased from 4.3:1 to 4.8:1 to 7.1:1, respectively (Table 3.2, entry 3, 4 and 5). However, further concentration to 2.0 M did not give a better result (Table 3.2, entry 6). Finally, by decreasing reaction temperature from 100 to 90 °C, the homoallylic alcohol product was formed in 78% yield with 7.5:1 *anti*-diastereoselectivity (Table 3.2, entry 5 and 7). Notably, the catalyst modified by 3,4-dinitrobenzoic acid was highly sensitive to reaction temperature, and under identical conditions at 90 °C, the homoallylic alcohol was produced in only 42% yield with 7.6:1 *anti*-diastereoselectivity (Table 3.2, entry 9).



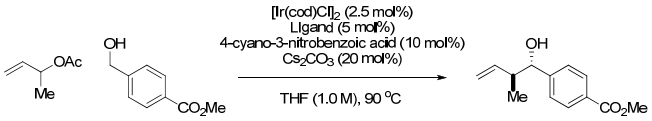
Entry	allyl acetate (eq)	THF (M)	T (°C)	Yield (%)	dr
1[a]	10	0.2	100	70	3.0:1
2	5	0.2	100	57	3.7:1
3	2	0.2	100	55	4.3:1
4	2	0.5	100	77	4.8:1
5	2	1.0	100	75	7.1:1
6	2	2.0	100	53	7.2:1
7	**2**	**1.0**	**90**	**78**	**7.5:1**
8	2	1.0	80	65	7.6:1
9[b]	2	1.0	80	42	7.6:1

[a] conducted by In Su Kim, [b] with 3,4-dinitrobenzoic acid

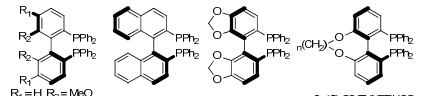
Table 3.2 Optimization of iridium catalyzed carbonyl croylation.

At this point, chirally modified catalysts were assayed (Table 3.3). Although catalysts incorporating the ligands (*S*)-BINAP, (*S*)-MeO-BIPHEP, and (*S*)-Cl,MeO-BIPHEP were found to enforce high levels of absolute stereocontrol, significant erosion

of diastereoselectivity was observed (Table 3.3, entries 1-3). Using a catalyst modified by (*S*)-SEGPHOS, the carbonyl crotylation product is formed in 70% isolated yield with 7.4:1 *anti*-diastereoselectivity and 95% enantiomeric excess (Table 3.3, entries 4). The TUNEPHOS ligands of Zhang[9] also were assayed (Table 3.3, entries 5-7). Here, (*S*)-C3-TUNEPHOS was found to provide the carbonyl crotylation product in 77% isolated yield with 8:1 *anti*-diastereoselectivity and 97% enantiomeric excess (Table 3.3, entry 6).



Entry	Ligand	Yield (%)	dr	ee%
1[a]	(*S*)-BINAP	75	3.5:1	95
2	(*S*)-MeO-BIPHEP	63	5.8:1	94
3[a]	(*S*)-Cl,MeO-BIPHEP	67	3.0:1	96
4	**(*S*)-SEGPHOS**	**70**	**7.4:1**	**95**
5	(*S*)-C2-TUNEPHOS	68	7.7:1	91
6[a]	**(*S*)-C3-TUNEPHOS**	**77**	**8.0:1**	**97**
7	(*S*)-C4-TUNEPHOS	71	6.4:1	92

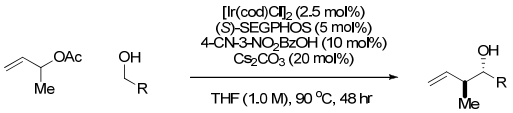


[a] conducted by In Su Kim

Table 3.3 Assay of chirally modified catalysts.

Having the optimized condition in hand, a range of alcohols was subjected to carbonyl crotylation (Table 3.4). In terms of scope, diverse substituted benzylic alcohols **3.1a-3.1f** were converted to the corresponding carbonyl crotylation products **3.3a-3.3f** in good to excellent yield, very good levels of *anti*-diastereoselectivity and with exceptional levels of absolute stereocontrol (Table 3.4, entries 1-5). Heteroaromatic alcohol **1.1f** also

gave the corresoponding product with excellent level of selectivity (Table 3.4, entry 6). As demonstrated by the conversion of cinnamyl alcohol **3.1g** to homoallylic alcohol **3.3g**, allylic alcohols also participate in the coupling (Table 3.4, entry 7). Finally, unactivated aliphatic alcohols **3.1h-3.1j** are transformed to the corresponding carbonyl crotylation products **3.3h-3.3j** in good yield with equally high levels of relative and absolute stereocontrol (Table 3.4, entries 8-10).



3.1a-3.1j (200 mol% / 100 mol%) → **3.3a-3.3j**

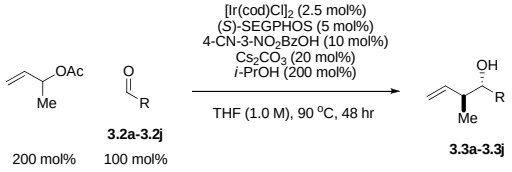
3.1a, R = Ph; **3.1b**, R = 3-MeOPh; **3.1c**, R = 4-MeOPh; **3.1d**, R = 4-BrPh; **3.1e**, R = 4-(CO_2Me)Ph
3.1f, R = 2-(*N*-Me-indole); **3.1g**, R = CH=CHPh; **3.1h**, R = 2-phenyl-1-ethyl; **3.1i**, R = 3-(benzyloxy)propyl; **3.1j**, R = $(CH_2)_7CH_3$

Entry	Alcohol	Product	Yield (%)	ee (%)	*anti:syn*
1	**3.1a**	**3.3a**	65	95	6:1
2	**3.1b**	**3.3b**	70	95	6:1
3[b]	**3.1c**	**3.3c**	67 73	90 92	5:1 4:1[c]
4	**3.1d**	**3.3d**	73	95	8:1
5[d]	**3.1e**	**3.3e**	70 77	95 97	7:1 8:1[c]
6[b]	**3.1f**	**3.3f**	73	95	5:1
7[d]	**3.1g**	**3.3g**	61 63	86 90	7:1 6:1[c]
8	**3.1h**	**3.3h**	69	97	7:1
9[d]	**3.1i**	**3.3i**	68	97	7:1
10[d]	**3.1j**	**3.3j**	69	97	7:1

[a] Reactions were performed in 13 x 100 mm pressure tubes. Cited yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis via comparison to racemic diastereomeric mixtures. See experimental section for further details. [b] 80 °C, 72 h. [c] (*S*)-C3-TUNEPHOS was used as ligand. d conducted by In So Kim

Table 3.4 Iridium catalyzed asymmetric crotylation from the alcohol oxidation level.

Carbonyl crotylation from the aldehyde oxidation level employing isopropanol as the terminal reductant also was explored (Table 3.5). To our delight, under conditions identical to those cited in Table 3.5, but in the presence of isopropanol (200 mol%), aryl aldehydes **3.2a**-**3.2f**, cinnamaldehyde **3.2g**, and unactivated aliphatic aldehydes **3.2h**-**3.2j** were converted to the corresponding carbonyl crotylation products **3.3a**-**3.3f** with complete levels of regioselectivity, very good levels of *anti*-diastereoselectivity and with exceptional levels of enantioselectivity. Thus, carbonyl crotylation was achieved from the aldehyde or alcohol oxidation level in the absence of preformed crotylmetal reagents.



3.2a-3.2j

200 mol% 100 mol%

3.3a-3.3j

3.2a, R = Ph **3.1b,** R = 3-MeOPh **3.1c**, R = 4-MeOPh **3.1d**, R = 4-BrPh **3.1e**, R = 4-(CO_2Me)Ph
3.2f, R = 2-(*N*-Me-indole) **3.1g**, R = CH=CHPh **3.1h**, R = 2-phenyl-1-ethyl **3.1i**, R = 3-(benzyloxy)propyl **3.1j**, R = $(CH_2)_7CH_3$

Entry	Aldehyde	Product	Yield (%)	ee (%)	*anti*:*syn*
1	**3.2a**	**3.3a**	77	98	9:1
2	**3.2b**	**3.3b**	74	98	9:1
3[b]	**3.2c**	**3.3c**	75 77	97 98	7:1 6:1[c]
4	**3.2d**	**3.3d**	78	97	11:1
5[d]	**3.2e**	**3.3e**	80 82	96 97	11:1 13:1[c]
6[b]	**3.2f**	**3.3f**	78	97	6:1
7[d]	**3.2g**	**3.3g**	66 68	98 98	7:1 8:1[c]
8	**3.2h**	**3.3h**	71	97	11:1
9[d]	**3.2i**	**3.3i**	68	97	11:1
10[d]	**3.2j**	**3.3j**	75	97	11:1

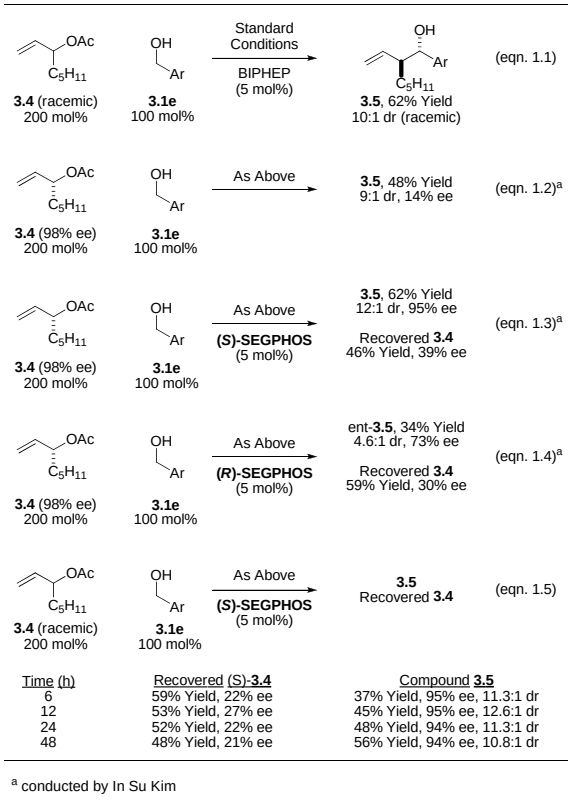
[a] Reactions were performed in 13 x 100 mm pressure tubes. Cited yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis via comparison to racemic diastereomeric mixtures. See experimental section for further details. [b] 80 °C, 72 h. [c] (*S*)-C3-TUNEPHOS was used as ligand.[d] conducted by In Su Kim

Table 3.5 Iridium catalyzed asymmetric crotylation from aldehyde oxidation level.

3.1.3 Mechanism Studies

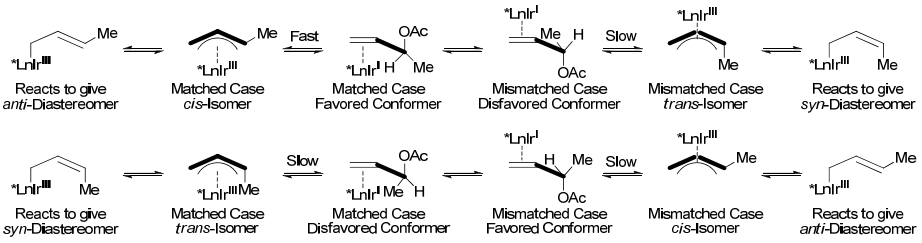
In prior studies of the parent allylation reaction,[9] intervention of symmetric iridium π-allyl intermediates or rapid interconversion of σ-allyl haptomers by means of a symmetric π-allyl was inferred on the basis of isotopic labeling studies. To evaluate the nature of the purported π-crotyl iridium intermediate, optically enriched allylic acetate **3.4** (98% ee) was coupled to alcohol **3.1e** under standard conditions employing the achiral ligand BIPHEP. The product, homoallylic alcohol **3.5**, was produced in 48% isolated yield with 9:1 *anti*-diastereoselectivity and 14% enantiomeric excess (Scheme 3.6, eqn. 1.2). These data suggest racemization via π-facial interconversion of the kinetic π-crotyl iridium complex occurs at a rate only marginally slower than the rate of carbonyl addition. To further probe the origins of stereoselection, optically enriched allylic acetate **3.4** (98% ee) was coupled to alcohol **3.1e** under standard conditions employing iridium catalysts modified by (*S*)-SEGPHOS and (*R*)-SEGPHOS (Scheme 3.6, eqn. 3 and 4, respectively). In the former case, excellent levels of relative and absolute stereocontrol were observed. In the later case, diminished efficiencies and reduced levels of diastereo- and enantioselectivity were evident. In both cases, recovered allylic acetate **3.4** exhibited significant erosion of optical purity. These experiments suggest that ionization of the (*R*)-allylic acetate **3.4** by the (*S*)-SEGPHOS modified iridium catalyst represents the lower energy diastereomeric pathway, that is, a stereochemically matched ionization mode. Partial racemization of recovered allylic acetate **3.4** suggests that ionization occurs reversibly with incomplete kinetic stereoselectivity. Finally, in reactions employing racemic allylic acetate **3.4** and the iridium catalyst modified by (*S*)-SEGPHOS, recovered

3.4 exhibited a substantial degree of optical enrichment favoring the (*S*)-enantiomer (Scheme 3.6, eqn. 5). This result is consistent with the notion that consumption of the (*R*)-allylic acetate **3.4** by the (*S*)-SEGPHOS modified iridium catalyst represents a more rapid stereochemically matched reaction pathway. Notably, the degree of optical enrichment of recovered (*S*)-**3.4** does not increase as a function of conversion due to erosion of the optical purity of unreacted allylic acetate **3.4** via reversible ionization, as was established in a preceding experiment (Scheme 3.6, eqn. 2).



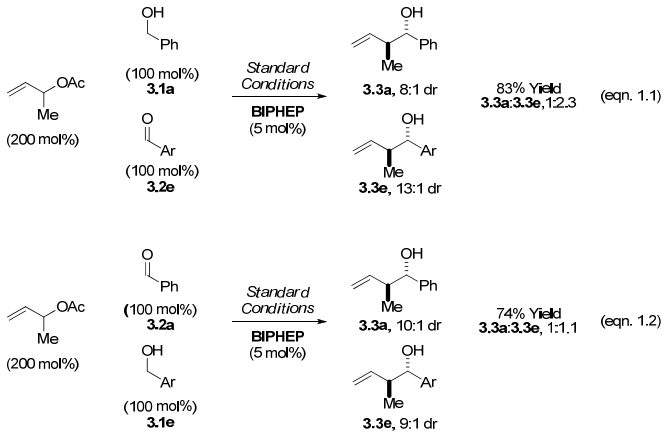
Scheme 3.6. Experiments aimed at probing the origins of stereoselection in Ir-catalyzed transfer hydrogenative crotylation (Ar = (4-(CO_2Me)Ph).

The observed *anti*-diastereoselectivity presumably arises via kinetic formation of the *cis*-π-crotyl complex,[10] which engages the carbonyl partner by way of an (*E*)-crotyl iridium intermediate (Scheme 3.7). Erosion of diastereoselectivity may result *via* isomerization to the *trans*-π-crotyl complex, which engages the carbonyl partner by way of the (*Z*)-crotyl iridium complex to form the *syn*-diastereomer. This interpretation may account for the fact that couplings to aldehydes exhibit uniformly higher levels of diastereoselectivity. For the aldehyde couplings, carbonyl addition is anticipated to be faster as higher concentrations of aldehyde are present throughout the course of the reaction, promoting rapid capture of the kinetic allyliridium intermediate. The observation that diastereoselectivity increases with increasing concentration in couplings of alcohols further supports the veracity of this interpretation.



Scheme 3.7. Stereochemical features associated with formation and isomerization of the purported crotyl iridium intermediates (*Ln = (*S*)-SEGPHOS and *C,O*-benzoate of 4-cyano-3-nitrobenzoic acid).

Exposure of α-methyl allyl acetate to equimolar quantities of **3.1a** and **3.2e** under standard conditions employing BIPHEP as ligand provided **3.3a** and **3.3e** in 83% yield in a 1:2.3 ratio, respectively. Exposure of α-methyl allyl acetate to equimolar quantities of **3.2a** and **3.1e** under otherwise identical conditions provided **3.3a** and **3.3e** in 74% yield in

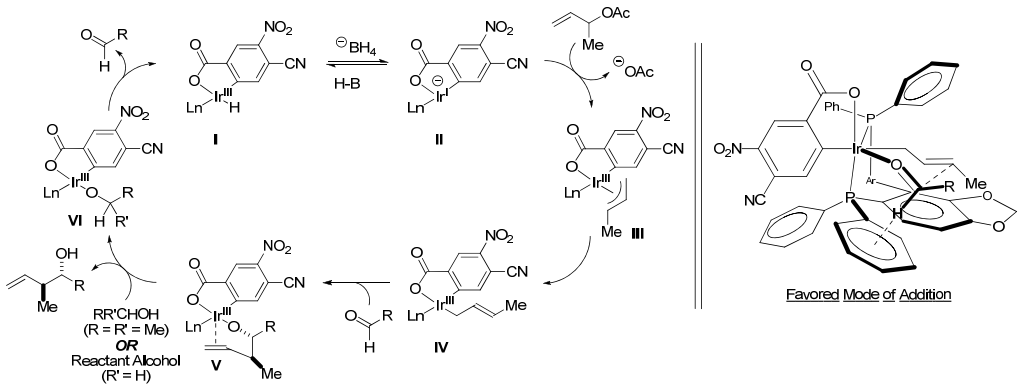


Scheme 3.8. Experiments establishing rapid redox equilibration in advance of carbonyl addition (Ar = (4-(CO_2Me)Ph).

a 1:1.1 ratio, respectively. These experiments demonstrate rapid redox equilibration in advance of carbonyl addition, which is relevant to crotylations conducted from the alcohol oxidation level (Scheme 3.8).

A simplified catalytic mechanism consistent with our collective results is depicted in Scheme 3.9. The *ortho*-cyclometallated iridium hydride **I** undergoes deprotonation in the presence of Cs_2CO_3 to furnish the anionic iridium(I) C,O-benzoate **II**.[11] Oxidative addition to α-methyl allyl acetate delivers the iridium π-crotyl complex **III**. The parent BINAP-ligated iridium π-allyl C,O-benzoate complex has been characterized by single-crystal X-ray diffraction and has been demonstrated to be catalytically relevant[9b] Aldehyde addition by way of the (*E*)-σ-crotyliridium complex **IV** through a closed chair-like transition structure delivers the *anti*-homoallyl iridium alkoxide **V**. This intermediate is stable with respect to β-hydride elimination of the carbinol C-H due to occupation of

the remaining coordination site at iridium(III) by the olefin moiety of the homoallylic alcohol. Exchange of the homoallylic alcohol for isopropanol or a reactant alcohol provides **VI**, which has an open coordination site and, consequently, *β*-hydride eliminates to regenerate the *ortho*-cyclometallated complex **I**. A stereochemical model accounting for the observed stereochemistry is analogous to that previously proposed (Scheme 3.9, right).



Scheme 3.9. Left: Simplified catalytic mechanism proposed for the iridium catalyzed transfer hydrogenative crotylation. Right: Model accounting for the observed sense of relative and absolute stereocontrol.

3.1.4 Summary

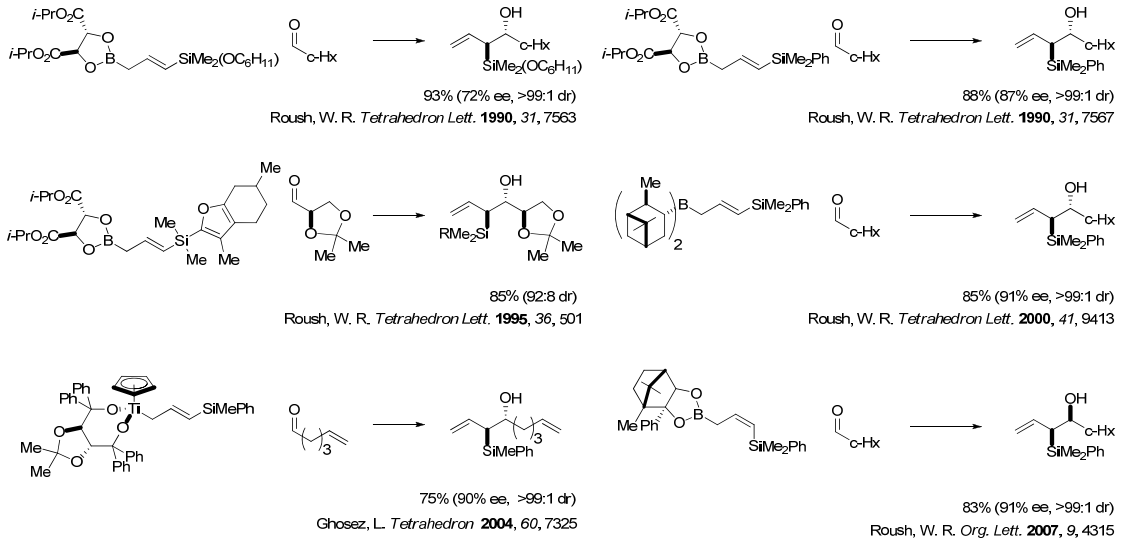
Anti-diastereo- and enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level under the conditions of iridium-catalyzed transfer hydrogenation was developed. This method circumvents the use of chirally modified crotylmetal reagents or metallic terminal reductants and, consequently, avoids generation of stoichiometric metallic byproducts. Furthermore, the ability to conduct carbonyl

crotylation directly from alcohol oxidation level allows one to bypass the oxidation chemistry typically required to convert alcohols to aldehydes.

3.2 ENANTIOSELECIVE IRIDIUM-CATALYZED CARBONYL SILYLALLYLATION

3.2.1 Background

A carbonyl silylallylation reaction has been attractive for many years due to the significance of the product as an important synthetic intermediate in organic reaction (Scheme 3.10).[12] For example, Roush utilized (*E*)-γ-(alkoxysilyl)allyl boronate for the construction of diols. Since then, various reagents have been developed from the same group to increase the selectivity. Recently, a chiral silyl allyl Titanium reagent was used to produce β-hydroxyallylsilanes with high reactivity and selectivity. These types of reagents share common drawbacks such as the generation of stoichiometric amounts of byproducts and multiple steps for preparation.

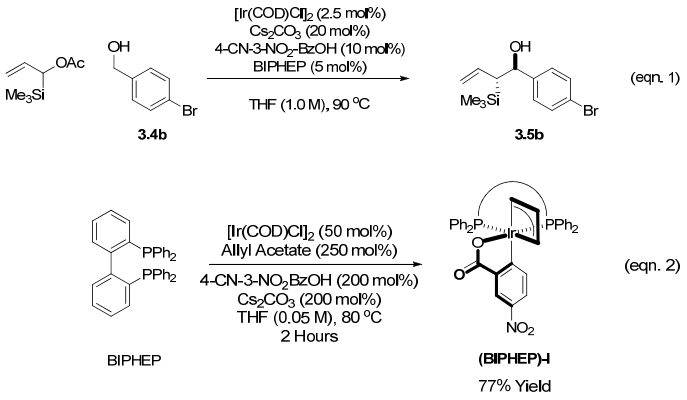


Scheme 3.10 Representative examples of chirally modified metal reagents for use in enantioselective carbonyl silylallylation.

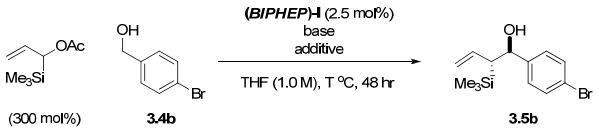
In connection with studies aimed at the discovery of hydrogen-mediated reductive C-C bond formations beyond hydroformylation, a broad family of C-C bond forming transfer hydrogenations promoted by iridium catalyst was reported.[13] A remarkable feature of these processes resides in the ability to achieve carbonyl addition from the aldehyde or alcohol oxidation level. In the former case, isopropanol or formic acid mediate reductive C-C coupling. In the latter case, dehydrogenation of the primary alcohol reactants generates aldehyde electrophiles, while simultaneously driving reductive generation of nucleophilic organometallics from unsaturated reactants. Unlike conventional methods for carbonyl allylation, these processes circumvent use of premetallated nucleophiles and metallic reductants. In this fashion, α-(trimethylsilyl)allyl acetate can serve as a alternative to previously reported silicon-containing 1,3- or 1,1-bimetallic allyl transfer agents.

3.2.2 Reaction optimization

Our study began with the attempted (trimethylsilyl)allylation of alcohol **3.4b**. Using the *ortho*-cyclometallated catalyst generated *in situ* from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, BIPHEP and allyl acetate, neither the desired (trimethylsilyl)allylation product **3.5b** nor resulting Peterson olefination product was detected (eqn. 1). Using the isolated π-allyl iridium precatalyst **(*BIPHEP*)-I** in the presence of Cs_2CO_3 (eqn. 2), the desired (trimethylsilyl)allylation product **3.5b** was formed along with substantial



quantities of Peterson olefination product. Having these preliminary results, various inorganic bases and reaction temperature were screened to suppress the Peterson olefination product (Table 3.6). After screening various inorganic bases, additives and temperatures, it was found that Peterson olefination was suppressed using K_3PO_4 (1.0 equiv.) in the presence of water (5.0 equiv.) for reactions conducted at 70 ^oC (Table 3.6, entry 9).



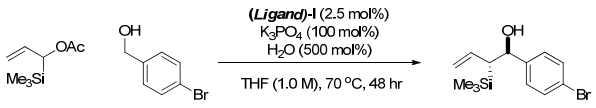
entry	base	additive	Temp.(^oC)	Yield(%)
1	Cs_2CO_3 (20 mol%)	-	90	5
2[a]	Na_2CO_3 (20 mol%)	-	90	20
3	Na_2CO_3 (50 mol%)	-	90	32
4	Na_2CO_3 (100 mol%)	-	90	41
5[a]	$NaHCO_3$ (100 mol%)	-	90	49
6	K_3PO_4 (100 mol%)	-	90	53
7[a]	K_3PO_4 (100 mol%)	H_2O (500 mol%)	90	60
8	K_3PO_4 (100 mol%)	H_2O (500 mol%)	80	65
9	K_3PO_4 (100 mol%)	H_2O (500 mol%)	70	72

[a] conducted by Xin Gao

Table 3.6 Optimization of inorganic base and temperature.

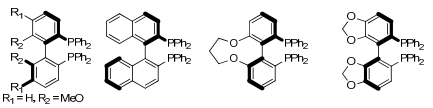
After identification of the reaction condition for *anti*-diastereoselective (trimethylsilyl)allylation, enantioselective variants of this process were explored. Accordingly, representative C_2-symmetric phosphine ligands were used to prepare a small set of chiral iridium *C*,*O*-benzoate complexes that were assayed for their ability to promote efficient *anti*-diastereo- and enantioselective (trimethylsilyl)allylation (Table 3.7).

The complex **(*Ligand*)-I** with (*R*)-SEGPHOS proved superior to all others assayed and was used to establish the reaction scope. Under these conditions, *α*-(trimethylsilyl)allyl acetate was coupled to a structurally diverse set of alcohols **3.4a**-**3.4i** (Table 3.8). In terms of scope, diverse substituted benzylic alcohols **3.4a**-**c** were converted to the corresponding carbonyl *α*-(trimethylsilyl)allylation products **3.5a**-**c** in good to excellent yield, very high levels of *anti*-diastereoselectivity and with exceptional



(300 mol%) **3.4b** **3.5b**

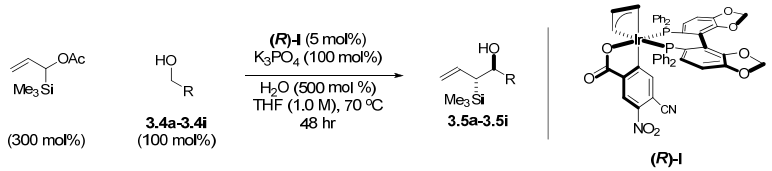
Entry	Ligand	Yield (%)	dr[a]	ee%[a]
1[b]	(*R*)-BINAP	43	≥99:1	96
2	(*R*)-MeO-BIPHEP	58	≥99:1	92
3[b]	(*R*)-Cl,MeO-BIPHEP	62	≥99:1	94
4	(*S*)-C3-TUNEPHOS	70	≥99:1	94
5	**(*S*)-SEGPHOS**	**72**	**≥99:1**	**96**



[a] dr and ee were determined by HPLC. [b] conducted by Xin Gao

Table 3.7 Assay of chirally modified catalysts.

levels of absolute stereocontrol (Table 3.8, entries 1-3). As demonstrated by the conversion of cinnamyl alcohol **3.4d** to homoallylic alcohol **3.5d**, allylic alcohols participate in the coupling (Table 3.8, entry 4). Heteroaromatic alcohol **3.4e** also gave the corresponding product with excellent level of selectivity (Table 3.8, entry 5). Finally, unactivated aliphatic alcohols **3.4f-i** were transformed to the corresponding products **3.5f-i** in good yield with equally high levels of relative and absolute stereocontrol (Table 3.8, entries 6-9).

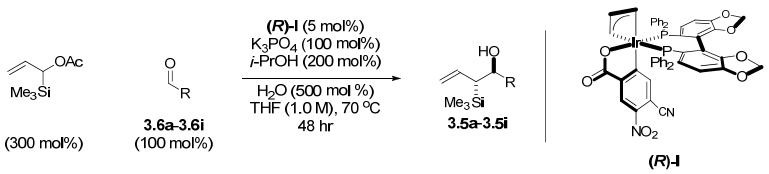


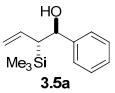
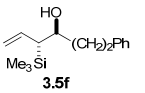
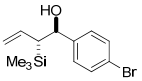
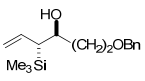
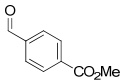
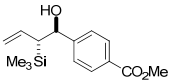
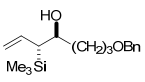
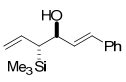
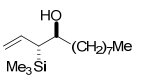
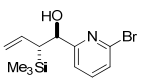
Entry	Alcohol	Product	Yield, dr, ee%	Entry	Alcohol	Product	Yield, dr, ee%
1	HO **3.4a**	HO Me3Si **3.5a**	69% Yield ≥ 99:1 dr 96% ee	6	HO (CH2)2Ph **3.4f**	HO (CH2)2Ph Me3Si **3.5f**	65% Yield ≥ 99:1 dr 97% ee
2	HO Br **3.4b**	HO Me3Si Br **3.5b**	72% Yield ≥ 99:1 dr 96% ee	7[a]	HO (CH2)2OBn **3.4g**	HO (CH2)2OBn Me3Si **3.5g**	61% Yield 98:2 dr 90% ee
3	HO CO2Me **3.4c**	HO Me3Si CO2Me **3.5c**	75% Yield ≥ 99:1 dr 98% ee	8[a]	HO (CH2)3OBn **3.4h**	HO (CH2)3OBn Me3Si **3.5h**	69% Yield ≥ 99:1 dr 95% ee
4[a]	HO Ph **3.4d**	HO Ph Me3Si **3.5d**	70% Yield ≥ 99:1 dr 92% ee[b]	9	HO (CH2)7Me **3.4i**	HO (CH2)7Me Me3Si **3.5i**	67% Yield ≥ 99:1 dr 95% ee
5[a]	HO N Br **3.4e**	HO N Br Me3Si **3.5e**	58% Yield ≥ 99:1 dr 99% ee				

[a] conducted by Xin Gao

Table 3.8 Enantioselective *α*-(trimethylsilyl)allylation from the alcohol oxidation level.

In the presence of isopropanol, but under otherwise identical conditions, α-(trimethylsilyl)allylation occurs from the aldehyde oxidation level to furnish an identical set of adducts **3.6a-i** (Table 3.9). Again, good isolated yields were accompanied by exceptional levels of diastereo- and enantioselectivity. Thus, unlike corresponding protocols involving allylmetal reagents,[12] carbonyl α-(trimethylsilyl)allylation occurs with equal facility from the alcohol or aldehyde oxidation level.

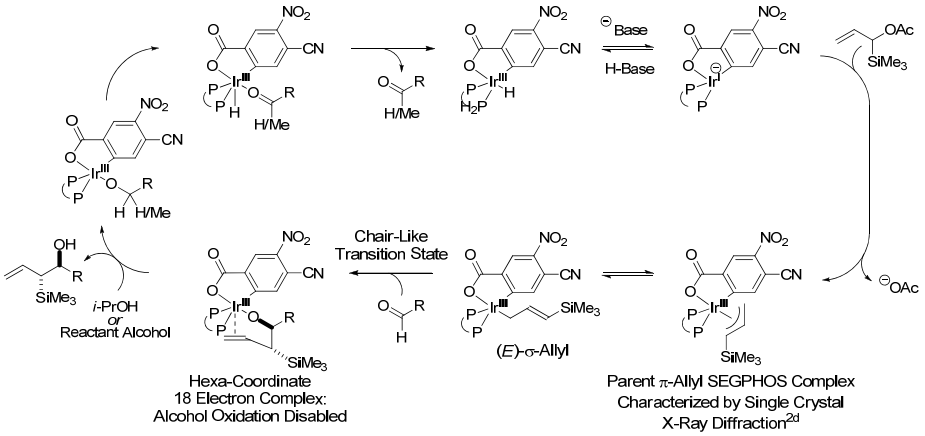


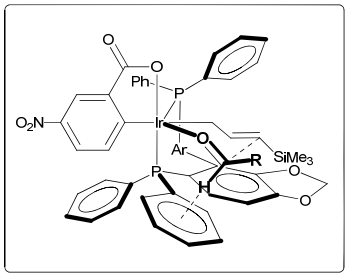
Entry	Alcohol	Product	Yield, dr, ee%	Entry	Alcohol	Product	Yield, dr, ee%
1	 **3.6a**	 **3.5a**	71% Yield ≥ 99:1 dr 96% ee	6	 **3.6f**	 **3.5f**	69% Yield ≥ 99:1 dr 98% ee
2	 **3.6b**	 **3.5b**	73% Yield ≥ 99:1 dr 98% ee	7[a]	 **3.6g**	 **3.5g**	63% Yield 4:1 dr 98% ee
3	 **3.6c**	 **3.5c**	78% Yield ≥ 99:1 dr 98% ee	8[a]	 **3.6h**	 **3.5h**	69% Yield ≥ 99:1 dr 98% ee
4[a]	 **3.6d**	 **3.5d**	74% Yield ≥ 99:1 dr 94% ee[b]	9	 **3.6i**	 **3.5i**	72% Yield ≥ 99:1 dr 90% ee
5[a]	 **3.6e**	 **3.5e**	66% Yield ≥ 99:1 dr 99% ee				

[a] conducted by Xin Gao

Table 3.9 Enantioselective α-(trimethylsilyl)allylation from the aldehyde oxidation level.

The mechanism for catalytic carbonyl (trimethylsilyl)allylation is analogous to that previously proposed for related crotylation.[14] However, complete levels of *anti*-diastereoselectivity were observed in nearly all cases, suggesting carbonyl addition occurs exclusively from the (*E*)-*σ*-allyl through a chair-like transition structure. Notably, although the catalyst dehydrogenated primary alcohols **3.4a**-**3.4i**, the reaction products **3.5a**-**3.5i**, which are homoallylic alcohols, were not oxidized under the coupling conditions and, hence, do not experience any erosion of enantiomeric purity by way of redox equilibration. This result is remarkable as 2-propanol, a secondary alcohol, was



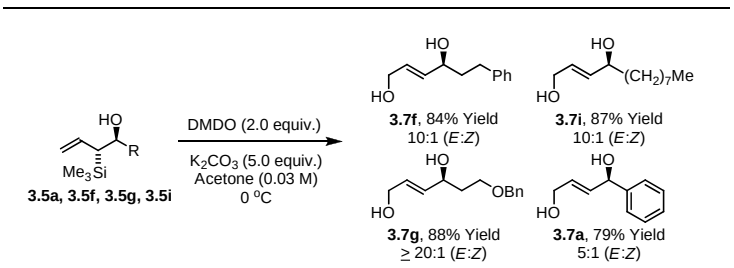


Scheme 3.11 Proposed catalytic mechanism and stereochemical model for carbonyl (trimethylsilyl)allylation from the alcohol or aldehyde oxidation level.

oxidized under the coupling conditions when aldehydes **3.6a-3.6i** were employed as reactants. As indicated in the proposed catalytic mechanism (Scheme 3.11), coordination of iridium to the homoallylic olefin of reaction products **3.5a-3.5i** provides a hexa-coordinate, 18-electron complex that cannot engage in β-hydride elimination due to the absence of an open coordination site.

3.2.3 Application

To evaluate the utility of the coupling products **3.5a-3.5i**, adducts **3.5a**, **3.5f**, **3.5g** and **3.5i** were subjected to DMDO-mediated oxidative elimination.[12l,m] The 1,4-ene-diols **3.7a**, **3.7f**, **3.7g** and **3.7i** were produced in excellent yield with high levels of *E*:*Z* selectivity (Scheme 3.12).

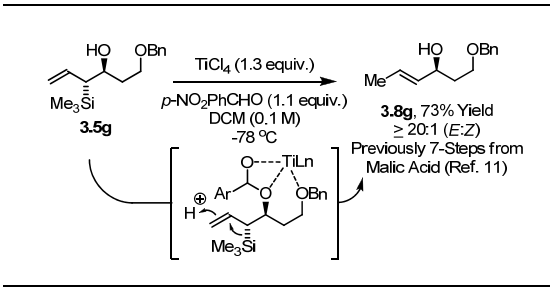


[a] conducted by Xin Gao

Scheme 3.12 Dioxirane mediated oxidative desilylation of adducts **3.5a**, **3.5f**, **3.5g** and **3.5i** to furnish the corresponding 1,4-ene-diols **3.7a**, **3.7f**, **3.7g** and **3.7i**.

Proto-desilylation was attempted next. Under nearly all conditions assayed, exclusive formation of Peterson olefination products was observed. However, upon exposure of adduct **3.5g** to $TiCl_4$ in the presence of exogenous aldehyde, the product of

proto-desilylation **3.8g** was generated in 73% yield with complete *E*:*Z* selectivity (Scheme 3.13). In the absence of aldehyde, Peterson olefination was again the exclusive reaction product, suggesting exogenous aldehyde protects the hydroxyl moiety of **3.5g** through formation of a titanium bound hemi-acetal. Notably, compound **3.8g** was previously prepared in 7-steps from malic acid.[15] Thus far, the protodesilylation is most efficient for the benzyl ether-containing adduct **3.5g**.

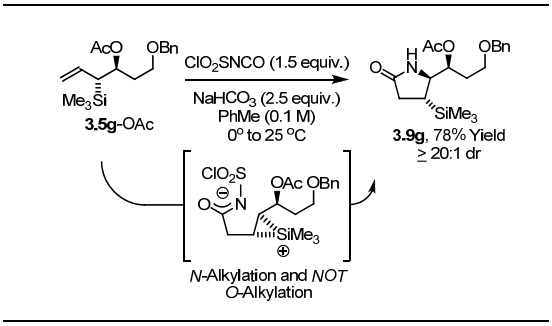


[a] conducted by Xin Gao

Scheme 3.13 Protodesilylation of **3.5g** requires exogenous aldehyde to suppress Peterson olefination.

Finally, under condition similar to those described by Woerpel,[16] exposure of **3.5g**-OAc to chlorosulfonyl isocyanate delivered the product of [3+2] cycloaddition, the 4,5-*trans*-disubstituted pyrrolidinone **3.9g**, as a single diastereomer. Lactone formation was not observed. Formation of the **3.9g** suggests a mechanism involving stereoselective addition of chlorosulfonyl isocyanate to the allylsilane *anti*-periplanar with respect to the silyl group to generate the indicated *β*-silyl carbocation. Exclusive *N*-cyclization accompanied by 1,2-silyl migration delivered the 4,5-*trans*-substituted pyrrolidinone

3.9g. In the absence of $NaHCO_3$, a mixture of lactone and lactam products was observed. These data suggest that partitioning of the *N*- and *O*-cyclization pathways is not dictated primarily by steric factors as proposed by Woerpel,[16b] but that the acidity of the medium plays a dominant role (Scheme 3.14)



[a] conducted by Xin Gao

Scheme 3.14 Reaction of adduct **3.5g** with chlorosulfonyl isocyanate to furnish the product of formal [3+2] cycloaddition **3.9g**.

3.2.4 Summary

In summary, a highly *anti*-diastereo- and enantioselective carbonyl (trimethylsilyl)allylation under the conditions of iridium catalyzed transfer hydrogenation employing a single-component catalyst, the *ortho*-cyclometallated complex **(*R*)-I** was reported. Notably, identical sets of adducts **3.5a-3.5i** were formed with comparable levels of selectivity from the aldehyde or alcohol oxidation level in the absence of Peterson olefination. Oxidative desilylation of adducts **3.5a**, **3.5f**, **3.5g** and **3.5i** employing DMDO provided access to highly enantiomerically enriched 1,4-ene-diols **3.7a**, **3.7f**, **3.7g** and

3.7i. Furthermore, conditions for proto-desilylation with allylic transposition have been identified for adduct **3.8g** in the absence of a hydroxyl protecting group. Finally, exposure of adduct **3.5g** to chlorosulfonyl isocyanate delivered 4,5-*trans*-disubstituted pyrrolidinone **3.9g** as a single diastereomer.

3.3 ENANTIOSELECIVE IRIDIUM-CATALYZED CARBONYL ALKOXYALLYLATION

3.3.1 Background

Among allylation protocols, enantioselective aldehyde α-alkoxyallylation provides an efficient means of generating allylic vicinal diol substructures. These vicinal diol structures are very common in many natural products (Figure 3.1).

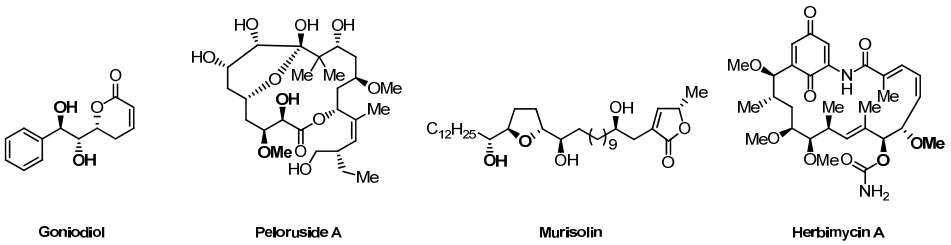
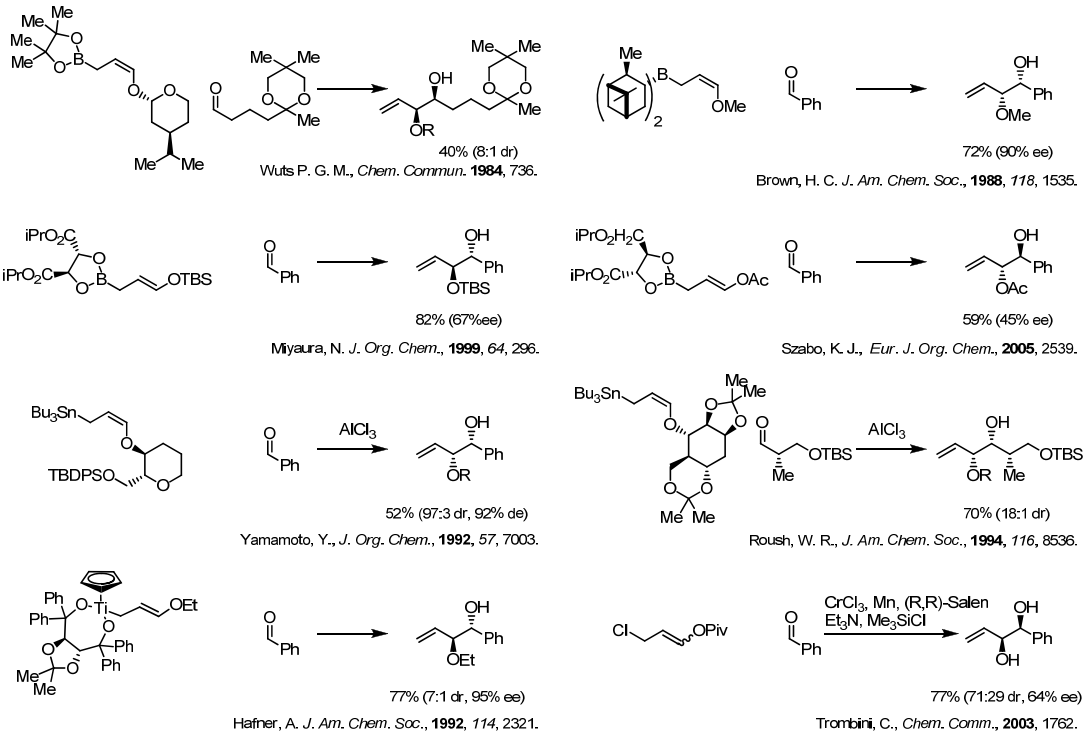


Figure 3.1 Representative vicinal diol motif containing natural products.

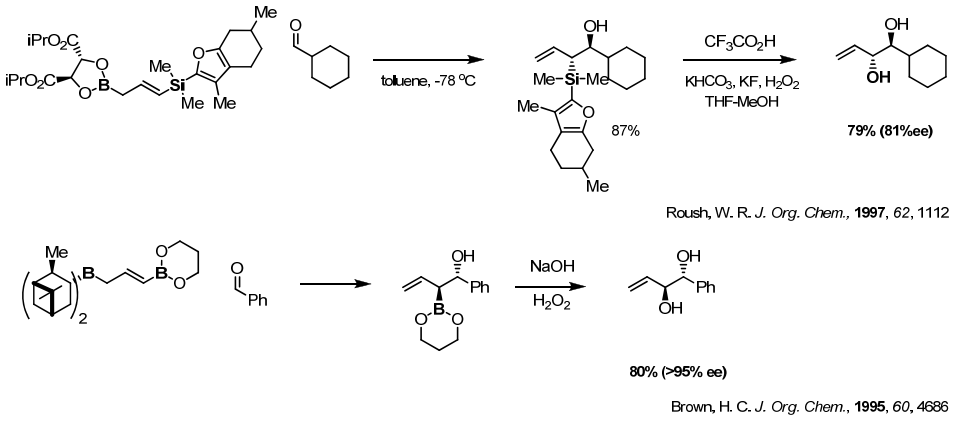
To date, asymmetric *syn*-additions of this type have employed chirally modified alkoxy-substituted allylmetal reagents based on boron,[17] aluminum,[18] titanium,[2i] indium,[19] or tin.[20] (Scheme3.15)

Indirect enantioselective aldehyde α-alkoxyallylation can be achieved using chirally modified reagents that promote aldehyde α-silylallylation or α-borylallylation followed by oxidation of the C-Si or C-B bond, respectively (Scheme 3.16).[21]

For direct methods, stereocontrolled access to *anti*-alkoxyallylation products is problematic because of difficulties encountered in the synthesis of the requisite *E*-configured allylmetal reagents.[22] This fact has motivated alternate approaches to the *anti*-1-ene-2,3-diol functional group array. For example, when enantioselective catalytic dihydroxylation of conjugated dienes was attempted,[23] *syn*-1-ene-2,3-diols were formed.

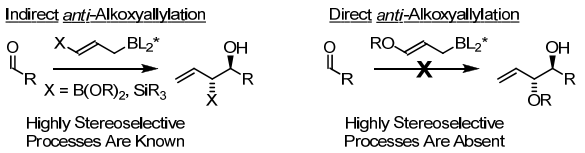


Scheme 3.15 Representative examples of chirally modified alkoxy-substituted allylmetal reagents for use in enantioselective carbonyl α-alkoxyallylation.



Scheme 3.16 Representative examples of indirect enantioselective aldehyde α-alkoxyallylation.

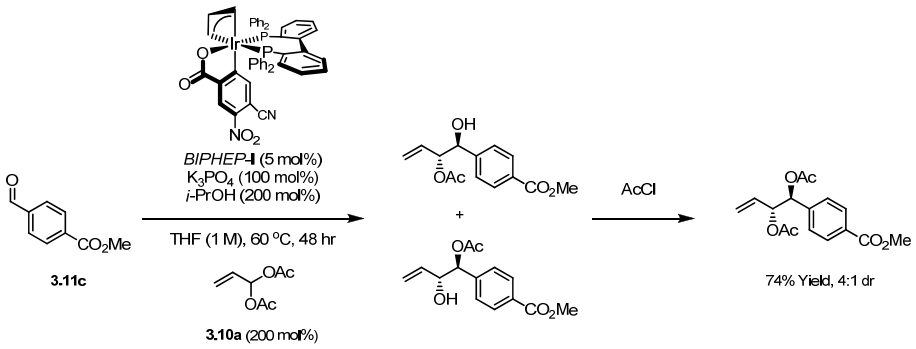
To our knowledge, only Duthaler's chiral allyltitanium reagent[2i] has been employed in direct enantioselective *anti*-alkoxyallylation; however, only a single highly stereoselective example was reported, and use of this allylmetal reagent is attended by considerable "preactivation".[24] To date, catalytic enantioselective methods for aldehyde *syn*-or *anti*-*α*-alkoxyallylation remain elusive.[25] Based on the iridium catalyzed entioselective allylation[2a,b,26] and crotylation reaction[14,27], enantioselective carbonyl *anti*-alkoxylation were sought.



3.3.2 Reaction optimization

In an initial experiment, acrolein *gem*-diacetate **3.10a** was subjected to isopropyl alcohol-mediated transfer hydrogenation in the presence of aldehyde **3.11c** employing the ortho-cyclometalated iridium *C*,*O*-benzoate **BIPHEP-I** derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, allyl acetate, and 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP). To our delight, the product of reductive coupling was obtained in 74% yield with complete branched regioselectivity as a 4:1 mixture of diastereomers favoring the *anti*-stereoisomer. Because partial migration of the acetyl moiety was observed under the reaction conditions, exhaustive acetylation was performed *in situ* upon complete

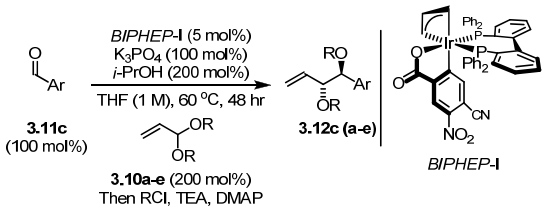
consumption of **3.11c**, and the product was isolated as the vicinal diacetate (Scheme 3.17).



Scheme 3.17 Initial alkoxyallylation of aldehydes employing *gem*-diacetate and acetylation.

In an effort to enhance the diastereoselectivity, a series of acrolein *gem*-dicarboxylates were assayed under identical conditions. It was hoped that a sufficiently large carboxy group would direct the partitioning of (*E*)- and (*Z*)-σ-allyl iridium intermediates to favor the (*E*)-σ-allyl isomer, which upon addition to the aldehyde through a Zimmerman-Traxler-type transition structure[28] would deliver the *anti*-diastereomer. Indeed, *gem*-dicarboxylates **3.10a-d**, which incorporate acetyl, propionyl, isobutyryl, and pivaloyl moieties, respectively, delivered products of alkoxyallylation with increasing levels of *anti*-diastereoselectivity. However, decreasing conversion in response to the increased steric demand of the carboxy moiety was observed. As earlier studies suggest that carbonyl addition is turnover-limiting,[14,29] it is likely that increased steric demand of the carboxy group impedes carbonyl addition. The best level of *anti*-

diastereoselectivity and conversion was observed using *gem*-dibenzoate **3.10e** (11:1 dr), perhaps because it is large enough to direct formation of the (*E*)-*σ*-allyl isomer yet does not impede approach of the aldehyde due to the flat topography of aromatic ring (Table 3.10).

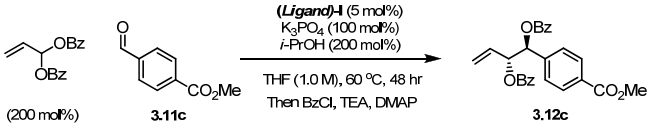


Entry	*gem*-Dicarboxylate	Yield of 3.12c (a-e)	Diastereomeric Ratio
1	**3.10a**, R = COMe	74%	4:1 dr (*anti:syn*)
2[a]	**3.10b**, R = COEt	65%	5:1 dr (*anti:syn*)
3[a]	**3.10c**, R = CO^{i}Pr	32%	8:1 dr (*anti:syn*)
4	**3.10d**, R = CO^{t}Bu	15%	10:1 dr (*anti:syn*)
5	**3.10e**, R = COPh	82%	11:1 dr (*anti:syn*)

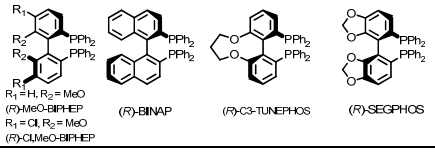
[a] conducted by Hoon Han

Table 3.10 Optimizing *anti*-diastereoselectivity in the alkoxyallylation of aldehydes employing *gem*-dicarboxylates derived from acrolein (Ar=*p*-PhCO$_2$Me).

After identification of acrolein *gem*-dibenzoate **3.10e** as an effective reagent for *anti*-diastereoselective alkoxyallylation, enantioselective variants of this process were explored. Accordingly, representative *C2*-symmetric phosphine ligands were used to prepare a small set of chiral iridium *C,O*-benzoate complexes that were assayed for their ability to promote efficient *anti*-diastereo- and enantioselective alkoxyallylation (Table 3.11).



Entry	Ligand	Yield (%)	dr[a]	ee%[a]
1	(*R*)-BINAP	41	13:1	97
2[b]	(*R*)-MeO-BIPHEP	63	10:1	91
3[b]	(*R*)-Cl,MeO-BIPHEP	60	9:1	92
4	(*S*)-C3-TUNEPHOS	71	11:1	95
5	**(*S*)-SEGPHOS**	**76**	**14:1**	**99**



[a] dr and ee were determined by HPLC and Chiral GC. [b] conducted by Hoon Han

Table 3.11 Assay of chirally modified catalysts.

The complex **(*R*)-SEGPHOS-I** proved superior to all others assayed and was used to establish the reaction scope. It was found that aromatic, heteroaromatic, *α,β*-unsaturated, and aliphatic aldehydes **3.11a-i** were converted to the corresponding alkoxyallylation products **3.12a-i** in good isolated yields (63-82%) with good to excellent diastereoselectivities (10:1 to 18:1 dr) and exceptional enantioselectivities (90-99% ee) (Table 3.12). Generation of the cyclometalated catalyst *in situ*, as previously reported,[14,29,30] led to poor isolated yields of product. In the absence of isopropyl alcohol, primary alcohols were not suitable substrates due to benzoyl transfer.

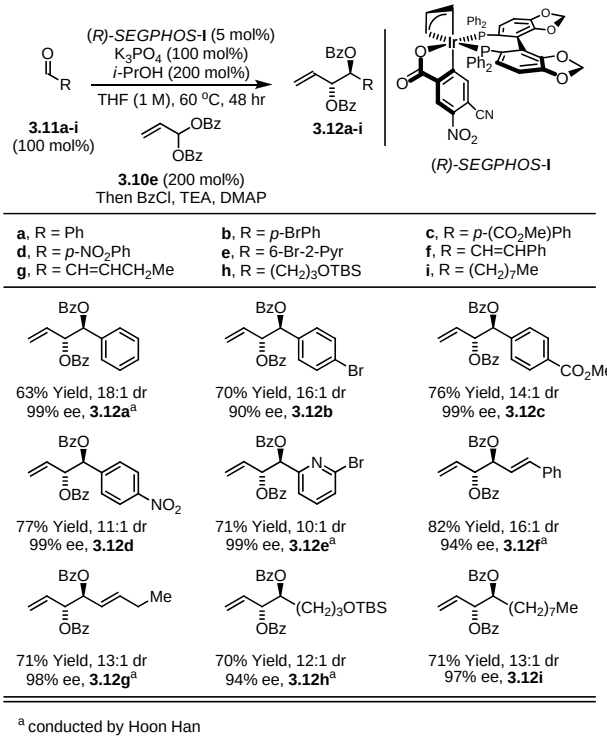
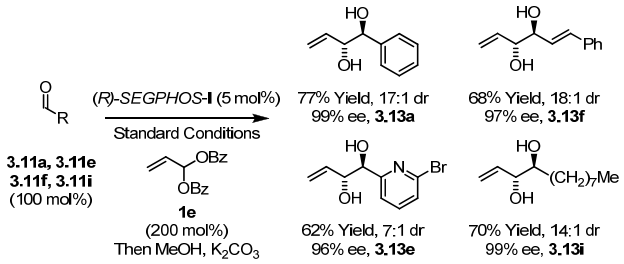


Table 3.12 *anti*-Diastereo and enantioselective alkoxyallylation of aldehydes employing *gem*-dibenzoate **3.10e** derived from acrolein.

To access the diol products directly, an alternate protocol involving saponification *in situ* was explored. Here, aldehydes **3.11a**, **3.11e**, **3.11f**, and **3.11i** were exposed to the standard reaction conditions employing *gem*-dibenzoate **3.10e** as the allyl donor. Upon complete consumption of the aldehyde, methanol and potassium carbonate were added to the reaction mixture. The diol-containing products **3.13a**, **3.13e**, **3.13f**, and **3.13i** were obtained in good isolated yields and with *anti*-diastereo- and enantioselectivities roughly equivalent with those observed for the corresponding dibenzoates **3.12a**, **3.12e**, **3.12f**, and **3.12i** (Scheme 3.18).



Scheme 3.18 *anti*-Diastereo and enantioselective alkoxyallylation of aldehydes to furnish diol products.

3.3.3 Summary

In summary, under the conditions of iridium-catalyzed transfer hydrogenation employing isopropyl alcohol as the terminal reductant, *gem*-dibenzoate **3.10e** reductively couples to aldehydes **3.11a-i** to furnish products of *anti*-alkoxyallylation with excellent relative and absolute stereocontrol. This protocol provides an alternative to the use of premetalated nucleophiles and chiral auxiliaries in asymmetric carbonyl alkoxyallylation, providing direct stereocontrolled access to the *anti*- 1-ene-2,3-diol functional group array under catalytic conditions.

3.4 ENANTIOSELECIVE IRIDIUM-CATALYZED CARBONYL REVERSEPRENYLATION

3.4.1 Background

The *gem*-dimethyl moiety is a very common structure in many natural products. For example, mycalamid A, epothilone, acutiphycin and bryostatin 1each have a *gem*-dimethyl moiety in their structures (Figure 3.2).

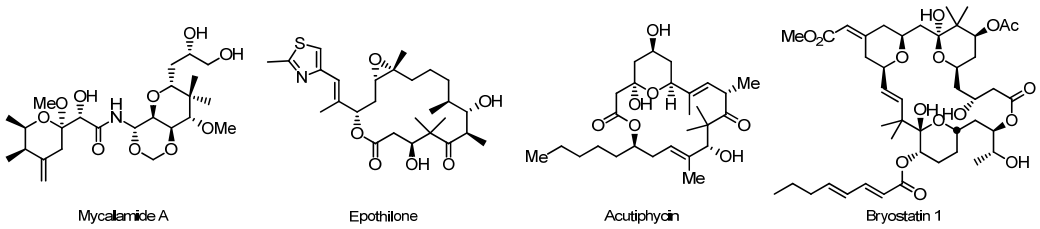
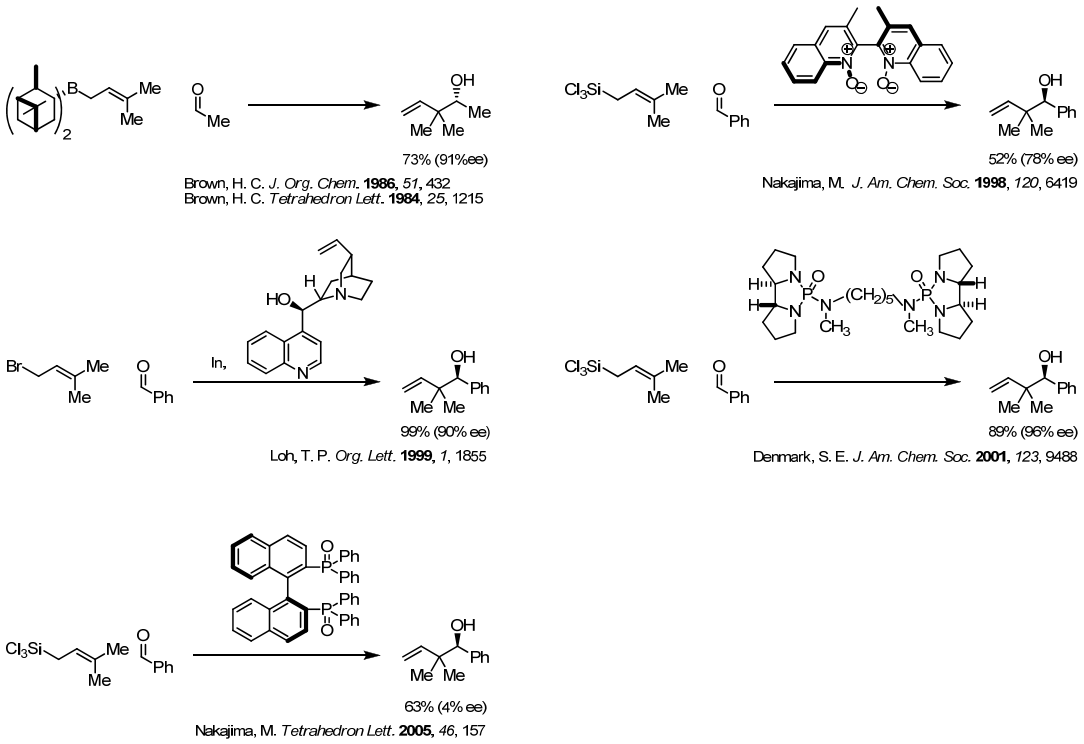


Figure 3.2 Representative natural products containing a *gem*-dimethyl motif.

Among the methods to construct *gem*-dimethyl, carbonyl prenylation has been extensively studied. However, most of the reactions were studied in the course of allylation reactions and only few reactions were conducted asymmetrically (Scheme 3.19).[31]

In the course of studies aimed at the development of C-C bond- forming hydrogenations, highly enantioselective carbonyl allylation[29,30], crotylation[14], (trimethylsilyl)allylation[32] and alkoxyallylation[33] employing various substituted allyl acetates were achieved under the conditions of iridium-catalyzed transfer hydrogenation. With catalytic asymmetric methods for polyacetate and polypropionate construction in hand, an asymmetric prenylation protocol was sought. This process could constitute an



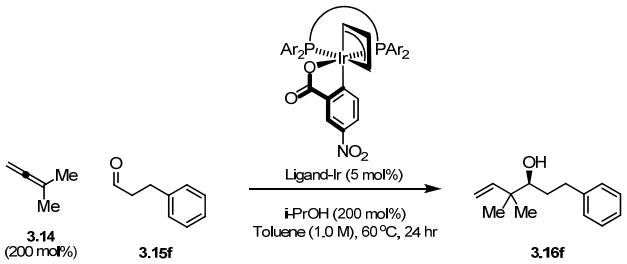
Scheme 3.19 Representative examples of enantioselective carbonyl reverseprenylation.

alternative to the use of stoichiometric metallic reagents in enantioselective carbonyl reverse prenylation.[31]

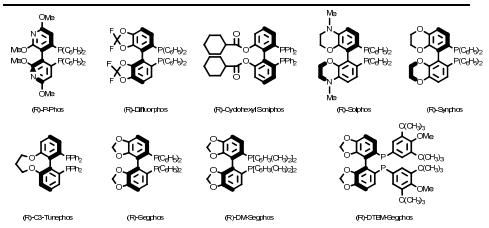
3.4.2 Reaction optimization

Attempted use of allylic acetates (2-methyl- 3-butenyl acetate or 3-methyl-2-butenyl acetate) as prenyl donors was unsuccessful. A potential solution to this problem resides in the use of 1,1-dimethylallene **3.14** as a prenyl donor. However, in earlier studies on the iridium-catalyzed reductive coupling of **3.14** to aldehydes mediated by

gaseous hydrogen, it was found that highly activated aldehydes were required, and despite an extensive assay of chiral phosphine ligands, only low levels of enantiomeric



Entry	Ligand	Yield(%)	ee(%)
1	(R)-P-Phos	trace	-
2	(R)-Difluorophos	22	64
3	(R)-Cyclohexy Soniphos	26	68
4[a]	(R)-Solphos	25	77
5[a]	(R)-Synphos	75	85
6	(R)-C3-Tunephos	73	83
7	**(R)-Segphos**	**70**	**87**
8[a]	(R)-DM-Segphos	72	82
9	(R)-DTBM-Segphos	20	56

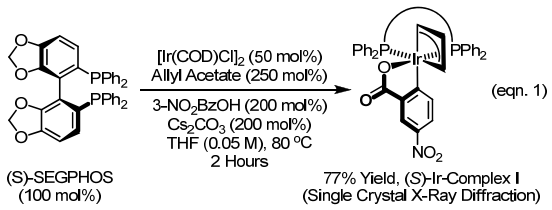


[a] conducted by In Su Kim

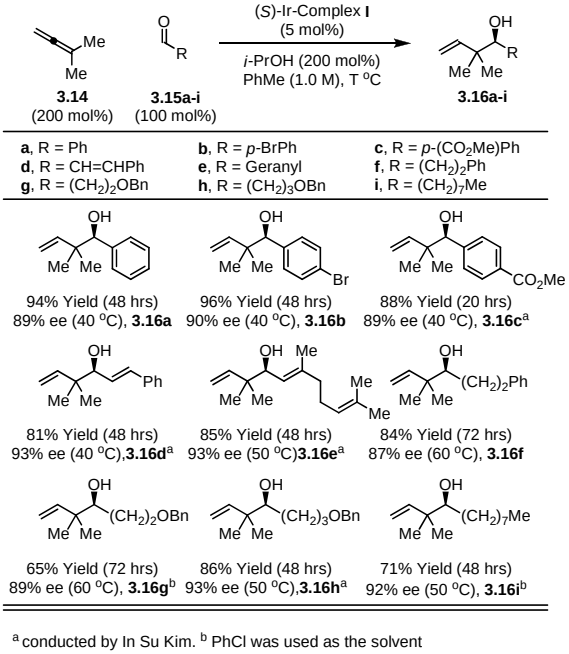
Table 3.13 Assay of chirally modified catalysts.

enrichment were observed.[34] To increase the enantioselectivity of the transformation, an ortho-cyclometalated iridium *C*,*O*-benzoate catalyst recently developed[32,33] was exploited for enantioselective catalytic carbonyl reverse prenylation employing **3.14** as the prenyl donor under transfer hydrogenation conditions. Various chiral ligand-Ir complexes were

synthesized and tested in the reverse prenylation reacdtion (Table 3.13). After extensive study involving an assay of commercial chelating chiral phosphine ligands, optimal results (70% yield, 87% ee, Table 3.13, entry 7) were achieved upon exposure of a toluene solution of **3.14** and **3.15f** to the cyclometalated iridium *C*, *O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid, and (S)-SEGPHOS,[35] designated "**(*S*)-Ir-Complex I**" (eqn. 1), in the presence of 2-propanol (200 mol %). In contrast to related allyl acetate-mediated allylations and crotylations, **3.14** couples at relatively low temperature in the absence of basic additives.



To explore the scope of this process, **3.14** was coupled to a structurally diverse set of aldehydes **3.15a-i** (Table 3.14). Aromatic aldehydes **3.15a-c**, α,β-unsaturated aldehydes **3.15d-e**, and aliphatic aldehydes **3.15f-i** were subject to reverse prenylation to furnish adducts **3.16a-i** in good to excellent isolated yields (65-96%) and enantioselectivities (87-93% ee).



[a] conducted by In Su Kim. [b] PhCl was used as the solvent

Table 3.14 Enantioselective carbonyl reverse prenylation from the aldehyde oxidation level.

In the absence of 2-propanol, enantioselective carbonyl reverse prenylation occurred directly from the alcohol oxidation level to furnish an identical set of adducts **3.16a-i**, once again with good to excellent isolated yields (68-94%) and enantioselectivities (86-91% ee) (Table 3.15). Especially noteworthy is the conversion of terpene **3.17e** to sequiterpene **3.16e** in the absence of any conventional preactivation of the reactants.

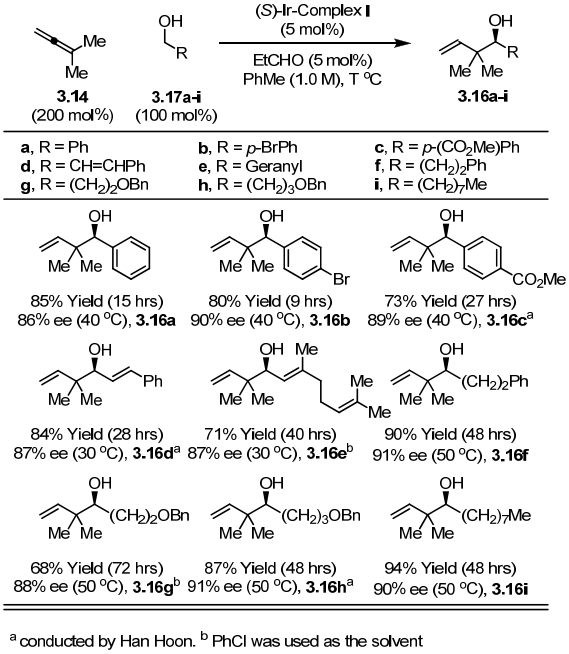
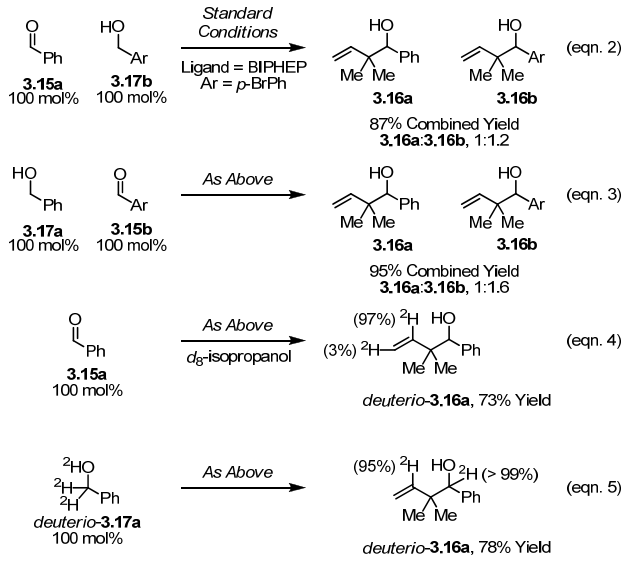


Table 3.15 Enantioselective carbonyl reverse prenylation from the alcohol oxidation level.

To gain further mechanistic insight, a crossover experiment was performed at 50 °C in the absence of 2-propanol using the achiral cyclometalated iridium *C*,*O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid, and BIPHEP. Exposure of **3.14** to equimolar quantities of **3.15a** and **3.17b** under the aforementioned conditions provided **3.16a** and **3.16b**, respectively, in 87% combined yield in a 1:1.2 ratio (eqn. 2 in Scheme 3.16). Exposure of **3.14** to equimolar quantities of **3.17a** and **3.15b** under otherwise identical conditions provided **3.16a** and **3.16b**, respectively, in 95% yield in a 1:1.6 ratio (eqn. 3 in Scheme 3.16). These experiments suggest rapid alcohol-aldehyde redox equilibration in advance of carbonyl addition. Isotopic labeling experiments also were performed at 50 °C using the achiral cyclometalated iridium *C*,*O*-benzoate derived from

allyl acetate, *m*-nitrobenzoic acid, and BIPHEP. When 2-propanol-d_8 was used as the terminal reductant, aldehyde **3.15a** was transformed to deuterio-**3.16a**, which incorporates deuterium at the interior vinylic position (97% ^{2}H) and the terminal vinylic position (3% ^{2}H) (eqn. 4 in Scheme 3.16). Use of deuterio-**3.17a** in the absence of 2-propanol delivered deuterio-**3.16a**, which incorporates deuterium at the interior vinylic position (95% ^{2}H) and the carbinol methine (>99% ^{2}H) (eqn. 5 in Scheme 3.16). High-fidelity incorporation of deuterium suggests that capture of the kinetically formed π-allyl complex is faster than reversible β-hydride elimination-hydrometalation.



Scheme 3.20 Isotopic labeling and competition experiments.

3.4.3 Summary

In summary, the first use of allenes in enantioselective C-C bond-forming transfer hydrogenation, as demonstrated by the development of an effective protocol for carbonyl reverse prenylation from the alcohol or aldehyde oxidation level have been reported.

3.5 ENANTIOSELECIVE IRIDIUM-CATALYZED ALLYLATION, CROTYLATION AND REVERSE PRENYLATION OF SUBSTITUTED ISATINS

3.5.1 Background

3-Substituted-3-hydroxy-oxindoles appear as substructures within a fascinating array of natural products, including the convulutamydines,[36 a,b] maremycins,[36c,d] donaxaridines,[36e,f] dioxibrassinins,[36g,h,i] celogentin K,[36j] hydroxyglucoisatisins[36k] and TMC-95A-D (Figure 3.3).[36l]

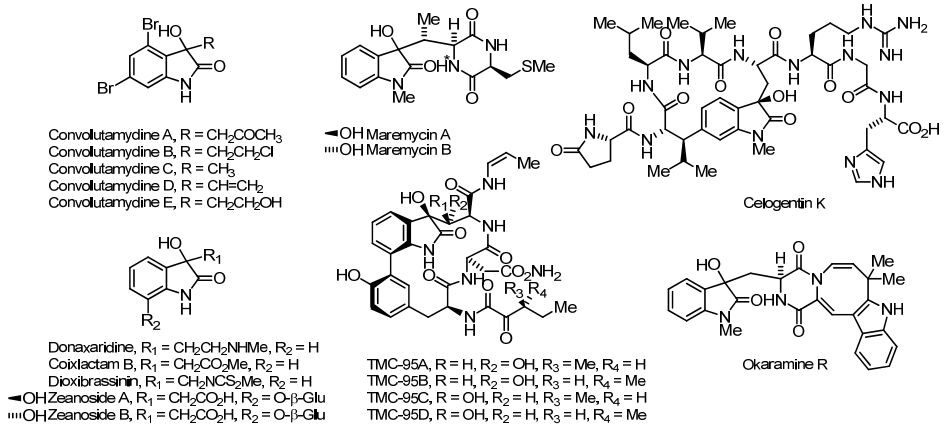


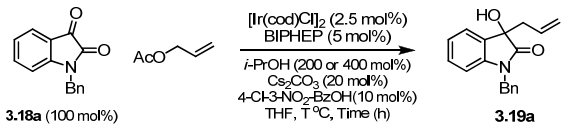
Figure 3.3 Examples of naturally occurring 3-substituted-3-hydroxy-oxindoles.

Whereas catalytic asymmetric additions to isatins are known,[37] highly enantioselective catalytic allylation, crotylation, and reverse prenylation of isatins have remained elusive. In the course of developing hydrogen-mediated C-C couplings beyond hydroformylation, chiral ortho-cyclometalated iridium *C*,*O*-benzoates were found to catalyze highly enantioselective carbonyl allylation,[29,30] crotylation,[14] and reverse prenylation[38] under transfer-hydrogenation conditions. In contrast to classical allylation

procedures which employ stoichiometric organometallic reagents, transfer-hydrogenation protocols exploit allyl acetate, α-methyl allyl acetate, and 1,1-dimethyl allene as precursors to transient allyl-, crotyl-, and prenyl metal intermediates, respectively. To further evaluate the scope of this emergent methodology, catalytic enantioselective additions to ketones were explored.

3.5.2 Reaction optimization

Our initial studies focused on the allylation of *N*-benzyl isatin **3.18a**. Using the cyclometalated *C*,*O*-benzoate generated in situ from $[Ir(cod)Cl]_2$, BIPHEP, and 4-chloro-3-nitrobenzoic acid, the coupling of allyl acetate (1000 mol%) to **3.18a** at 100 °C in THF (0.2 M) delivered the tertiary homoallylic alcohol **3.19a** in 42% yield upon isolation (Table 3.16, entry 1). At lower loadings of allyl acetate (200 mol%) with higher reaction temperature (120 °C) and extended reaction time (43 hr), the yield of homoallylic alcohol **3.19a** was increased to 69% (Table 3.17, entry 4). Further optimization of reaction concentration gave the product **3.19a** with 77% yield (Table 3.16, entry 6).



3.18a (100 mol%) **3.19a**

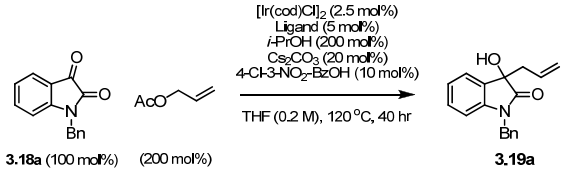
Entry	Allyl Acetate	[THF]	T °C	Time	Yield (%)
1[a]	1000 mol%	0.2 M	100	19 hr	42
2[a]	200 mol%	0.2 M	100	19 hr	37
3[a]	200 mol%	0.2 M	120	19 hr	54
4	200 mol%	0.2 M	120	43 hr	69
5	200 mol%	0.5 M	120	43 hr	49
6	**200 mol%**	**0.1 M**	**120**	**43 hr**	**77**

[a] conducted by Junji Itoh

Table 3.16 Allylation of *N*-benzyl isatin **3.18a**.

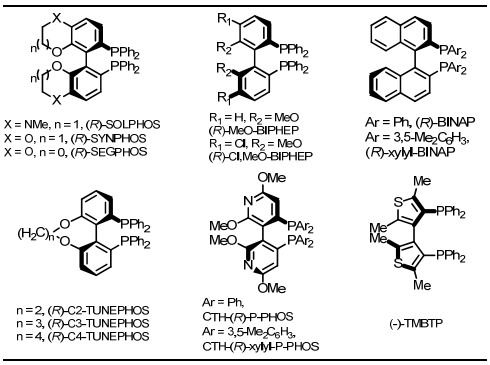
Having these results in hand, an assay of chelating chiral phosphine ligands was undertaken. (*R*)-BINAP liagnd produced **3.19a** with 47% yield and 79% ee.(Table 3.17, entry 1) Among the various chiral ligands screening, CTH-(*R*)-P-PHOS gave the best selectivity (81% ee) and reactivity (78% yield) (Table 3.17, entry 14). However, the selectivity was not satisfactory and further optimization was necessary.

Changing additive from 4-Cl-3-NO_2-BzOH to 4-CN-3-NO_2-BzOH showed better reactivity (Table 3.18, entry 2). Decreasing the reaction temperature revealed dramatic enhancement in the level of asymmetric induction (92% ee). However, lower temperatures also diminished conversion to 53% yield (Table 3.18, entry 3). This impasse was resolved by increasing the loading of isopropanol from 200 mol% to 400 mol%, which enabled conversion of *N*-benzyl isatin **3.18a** to the homoallylic alcohol **3.19a** in 73%yield and 91% enantiomeric excess using cth-(*R*)-p-phos (cth-(*R*)-p-phos = (*R*)-(+)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenyl-phosphino)-3,3'-bipyridine) as the ligand. Notably, under analogous reaction conditions employing our initially disclosed iridium catalyst modified by 3-nitrobenzoic acid, **3.19a** was obtained in 61%yield and 90% enantiomeric excess. These data further illustrate how catalyst performance is enhanced through structural variation of the *C*,*O*-benzoate moiety.



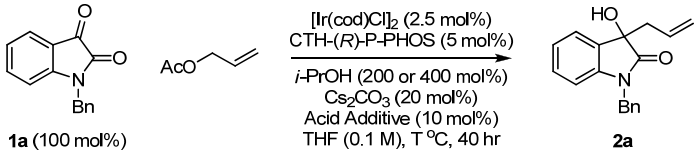
3.18a (100 mol%) (200 mol%) **3.19a**

Entry	Ligand	Yield (%)	ee (%)
1[a]	(*R*)-BINAP	47	79 (*R*)
2	(*R*)-tol-BINAP	49	79 (*R*)
3[a]	(*S*)-SEGPHOS	74	69 (*S*)
4[a]	(*R*)-DM-SEGPHOS	59	27 (*R*)
5[a]	(*R*)-SYNPHOS	78	68 (*R*)
6	(*R*)-SOLPHOS	73	62 (*R*)
7	(-)-TMBTP	68	78 (*R*)
8[a]	(*R*)-MeO-BIPHEP	78	71 (*R*)
9	(*R*)-Cl,MeO-BIPHEP	63	79 (*R*)
10[a]	(*R*)-C_2-TUNEPHOS	72	57 (*R*)
11	(*R*)-C_3-TUNEPHOS	67	65 (*R*)
12	(*R*)-C_4-TUNEPHOS	55	59 (*R*)
13	CTH-(*R*)-xylyl-P-PHOS	42	39 (*R*)
14[a]	**CTH-(*R*)-P-PHOS**	**78**	**81 (*R*)**



[a] conducted by Junji Itoh

Table 3.17 Assay of chiral ligands in allylation reaction.

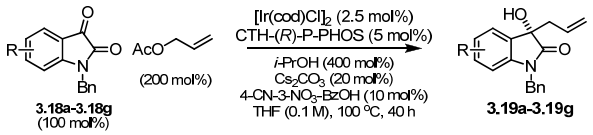


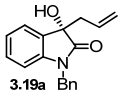
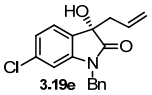
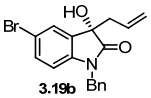
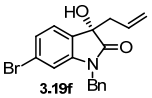
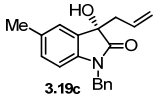
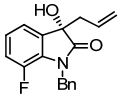
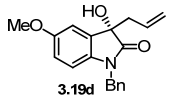
1a (100 mol%) **2a**

Entry	Ligand	Acid Additive	*i*-PrOH	T °C	Yield (%)	ee (%)
1	CTH-(*R*)-P-PHOS	4-Cl-3-NO_2-BzOH	200 mol%	120	78	81 (*R*)
2	CTH-(*R*)-P-PHOS	4-CN-3-NO_2-BzOH	200 mol%	120	85	82 (*R*)
3	CTH-(*R*)-P-PHOS	4-CN-3-NO_2-BzOH	200 mol%	100	53	92 (*R*)
4	**CTH-(*R*)-P-PHOS**	**4-CN-3-NO_2-BzOH**	**400 mol%**	**100**	**73**	**91 (*R*)**

Table 3.18 Optimization of allylation reaction.

Optimal reaction conditions identified for the conversion of *N*-benzyl isatin **3.18** to the hydroxy oxindole **3.19a** were applied to substituted isatins **3.18a**–**3.18g** (Table 3.19). Various 5, 6 and 7-substituted groups on the aromatic ring were tested. For example, 5-bromo substituted isatin **3.18b** gave 83% yield of the corresponding product **3.19b** with excellent selectivity (95 %ee) (Table 3.19, entry 2). Electron donating groups such as 5-methyl **3.18c** and methoxy substitution **3.18d** produce the products with great reactivity and selectivity (Table 3.19, entry 3, 4). Substitution on 6, 7 (**3.18e-g**) also produce the alcohol with high yield and excellent selectivity (Table 3.19, entry 5, 6 and 7). The absolute stereochemical assignments of the adducts **3.19a**–**g** are based upon that



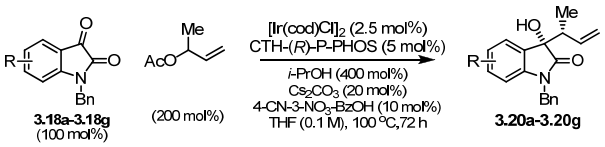
entry	Product	yield (%)	ee (%)	entry	Product	yield (%)	ee (%)
1[d]	 **3.19a**	74	91	5[d]	 **3.19e**	73	96
2[b,d]	 **3.19b**	83	94	6[b,d]	 **3.19f**	80	94
3[d]	 **3.19c**	89	92	7[c]	 **3.19g**	65	93
4	 **3.19d**	92	92				

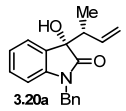
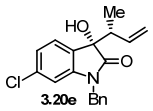
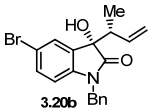
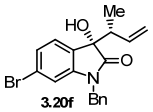
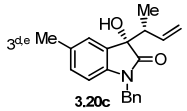
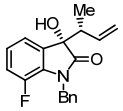
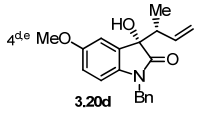
[a]All reactions were performed in 13 x 100 mm pressure tubes. Cited yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See supporting information for further details. [b]10 mol% loading of Cs_2CO_3 was used and the reaction was conducted for 72 hours. [c]400 mol% loading of allyl acetate was used.[d] conducted by Junji Itoh.

Table 3.19 Catalytic enantioselective allylation *N*-benzyl isatins **3.18a-g** *via* iridium catalyzed C-C bond forming transfer hydrogenation.

determined for the 5-bromo derivative **3.19b** by single-crystal X-ray diffraction analysis using the anomalous dispersion method.

Given these favorable results, the crotylation of substituted isatins **3.18a**–**g** was attempted under identical conditions employing α-methyl allyl acetate as the crotyl donor (Table 3.20). The products of ketone crotylation, **3.20a**–**g,** were produced in moderate to excellent yields upon isolation (64–87%) with moderate to excellent levels of optical enrichment (80–92%ee). In general, crotylation required longer reaction times (Table 3.20, entries 1, 2, and 5–7). Additionally, it was found that lower loadings of Cs_2CO_3



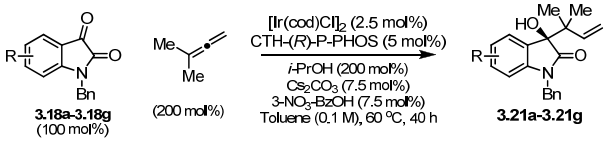
entry	Product	yield (%)	ee (%)	d.r.	entry	Product	yield (%)	ee (%)	d.r.
1[b,g]	 **3.20a**	74	91	13:1	5[b,g]	 **3.20e**	73	96	19:1
2[f,g]	 **3.20b**	83	94	16:1	6[f,g]	 **3.20f**	80	94	15:1
3[d,e]	 **3.20c**	89	92	18:1	7[b,c]	 **3.20g**	65	93	19:1
4[d,e]	 **3.20d**	92	92	29:1					

[a]As described in Table 3.20 footnotes. [b]10 mol% loading of Cs_2CO_3 was used. [c]400 mol% loading of allyl acetate was used. [d]The reaction was run for 40 hr. [e]Me-THF was used as the solvent.[f] 5 mol% loading of $[Ir(cod)Cl]_2$, 10 mol% of cth-(*R*)-p-phos, and 20 mol% loading of 4-CN-3-NO_2-BzOH were used.[g] conducted by Junji Itoh.

Table 3.20 Catalytic enantioselective crotylation of *N*-benzyl isatins **3.18a**–**g** by iridium-catalyzed C-C bond-forming transfer hydrogenation.

increased conversion in certain cases (Table 3.20, entries 1, 5 and 7). The absolute stereochemical assignment of adducts **3.20a**–**g** are based upon that determined for the 5-bromo derivative **3.20b** by single-crystal X-ray diffraction analysis using the anomalous dispersion method.

Finally, the reverse prenylation of substituted isatins **3.18a–g** was attempted (Table 3.21). To our delight, adducts **3.21a–g** were generated in uniformly high yields (70–90%) and high levels of optical enrichment (90–96%ee) under mild reaction conditions. Notably, this transformation enables the creation of two contiguous quaternary carbon centers. The absolute stereochemical assignment of adducts **3.21a**–**4g**



3.18a-3.18g (100 mol%)

3.21a-3.21g

entry	Product	yield (%)	ee (%)	entry	Product	yield (%)	ee (%)
1	**3.21a**	90	96	5	**3.21e**	80	93
2	**3.21b**	86	90	6[b]	**3.21f**	70	93
3	**3.21c**	79	93	7[b]	**3.21**	79	94
4	**3.21d**	81	96				

[a]As described in Table 1 footnotes. [b]The reaction was run for 72 h

Table 3.21 Catalytic enantioselective prenylation of *N*-benzyl isatins **3.18a**–**g** by iridium-catalyzed C-C bond-forming transfer hydrogenation.

are based upon that determined for the 5-bromo derivative **3.21b** by single- crystal X-ray diffraction analysis using the anomalous dispersion method.

3.5.3 Summary

In summary, the first enantioselective allylations, crotylations, and prenylations of isatin, which are achieved by isopropanol-mediated transfer hydrogenation, was reported. Unlike conventional allylation methodologies which employ stoichiometric quantities of allyl–metal reagents, the present method exploits allyl acetate, *α*-methyl allyl acetate, and 1,1-dimethylallene as precursors to transient allyl-, crotyl-, and prenyl metal intermediates, respectively. To our knowledge, these studies represent the first examples of catalytic enantioselective ketone allylation, crotylation, and prenylation in the absence of stoichiometric amounts of allylmetal reagents.

3.6 EXPERIMENTAL SECTIONS

General procedure for *anti*-Diastereo- and Enantioselective Crotylation from the Alcohol Oxidation Level

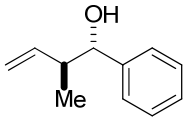
To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), (*S*)-SEGPHOS (12.2 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by acetic acid 3-buten-2-yl ester (91.3 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to room temperature. Alcohol substrate (0.4 mmol, 100 mol%) in THF (0.2 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography provided the corresponding product.

General procedure for *anti*-Diastereo- and Enantioselective Crotylation from the Aldehyde Oxidation Level

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), (*S*)-SEGPHOS (12.2 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by acetic acid 3-buten-2-yl ester (91.3 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to room temperature. Aldehyde substrate (54.5 mg, 0.4 mmol, 100

mol%) in THF (0.2 mL) and isopropanol (59.8 μL, 0.8 mmol, 200 mol%) were added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography provided the corresponding product.

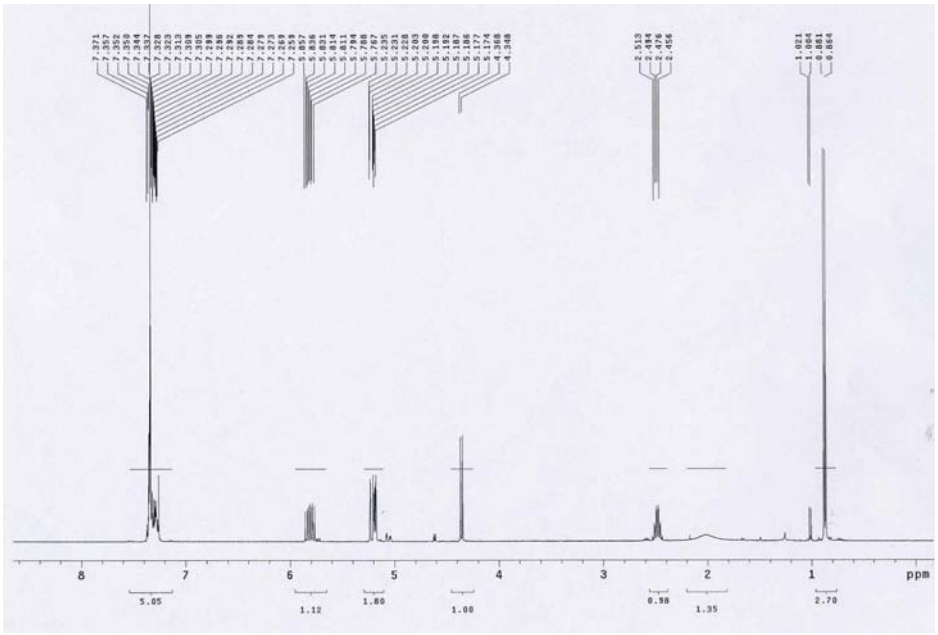
(1*S*,2*S*)-2-Methyl-1-phenylbut-3-en-1-ol



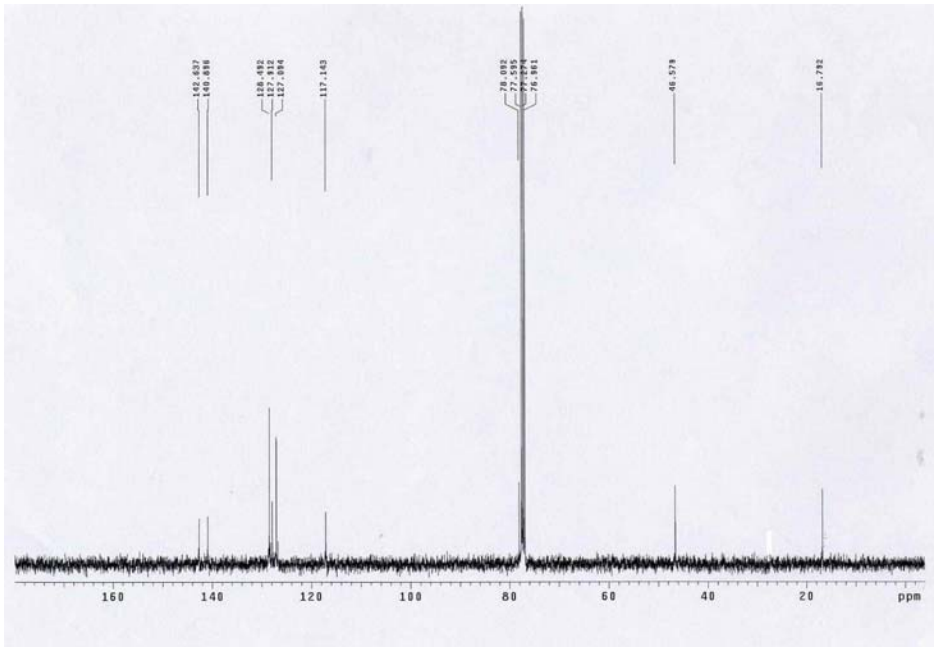
3.3a

TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5H), 5.86-5.76 (m, 1H), 5.24-5.17 (m, 2H), 4.35 (d, *J* = 8.0 Hz, 1H), 2.52-2.45 (m, 1H), 2.07 (br s, 1H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.9, 128.5, 127.9, 127.1, 117.1, 78.1, 46.6, 16.8. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), t_{major} = 27.5 min, t_{minor} = 30.8 min; ee = 95% (alcohol), 98% (aldehyde).

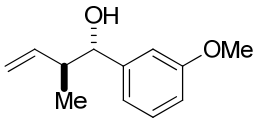
^{1}H NMR



^{13}C NMR



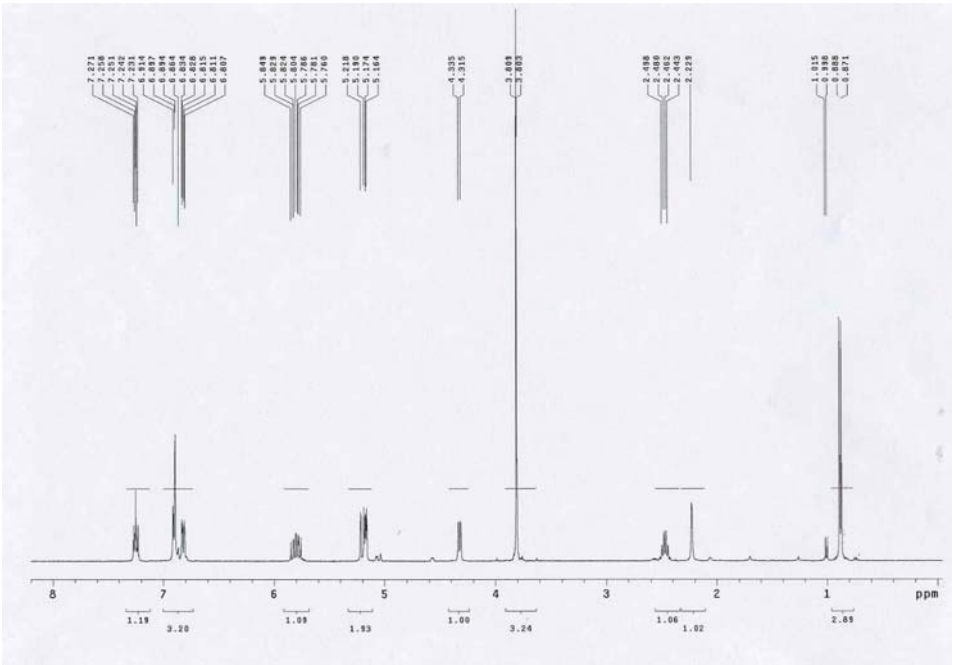
(1*S*,2*S*)-1-(3-Methoxyphenyl)-2-methylbut-3-en-1-ol



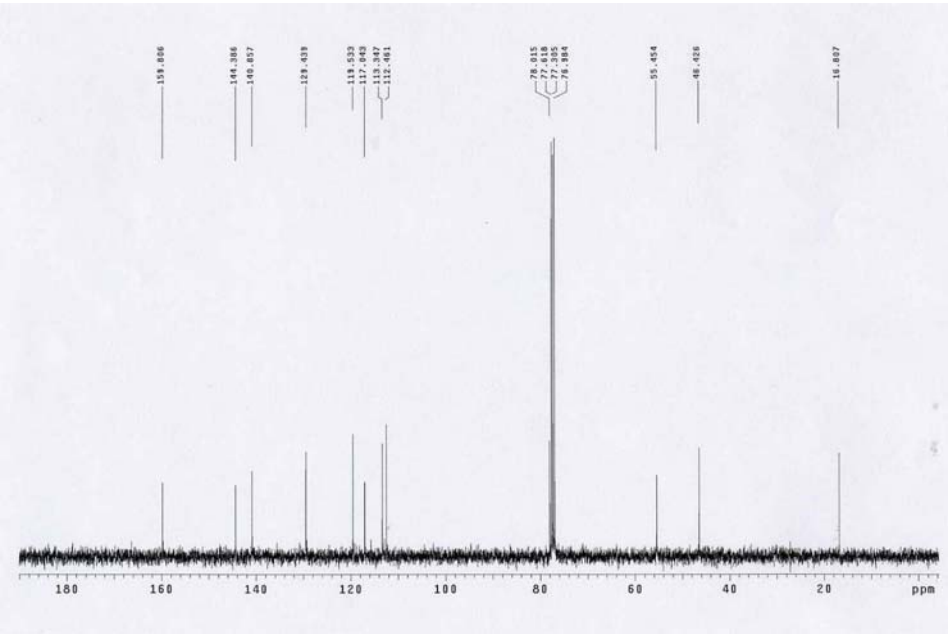
3.3b

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 1H), 6.92-6.80 (m, 3H), 5.85-5.76 (m, 1H), 5.22-5.16 (m, 2H), 4.32 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.50-2.44 (m, 1H), 2.22 (br s, 1H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 144.4, 140.9, 129.4, 119.5, 117.0, 113.3, 112.5, 78.0, 55.5, 46.4, 16.8. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 96:4, 0.5 mL/min, 254 nm), t_{minor} = 24.5 min, t_{major} = 28.0 min; ee = 95% (alcohol), 98% (aldehyde).

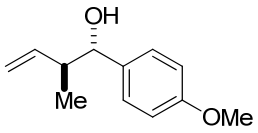
^{1}H NMR



^{13}C NMR



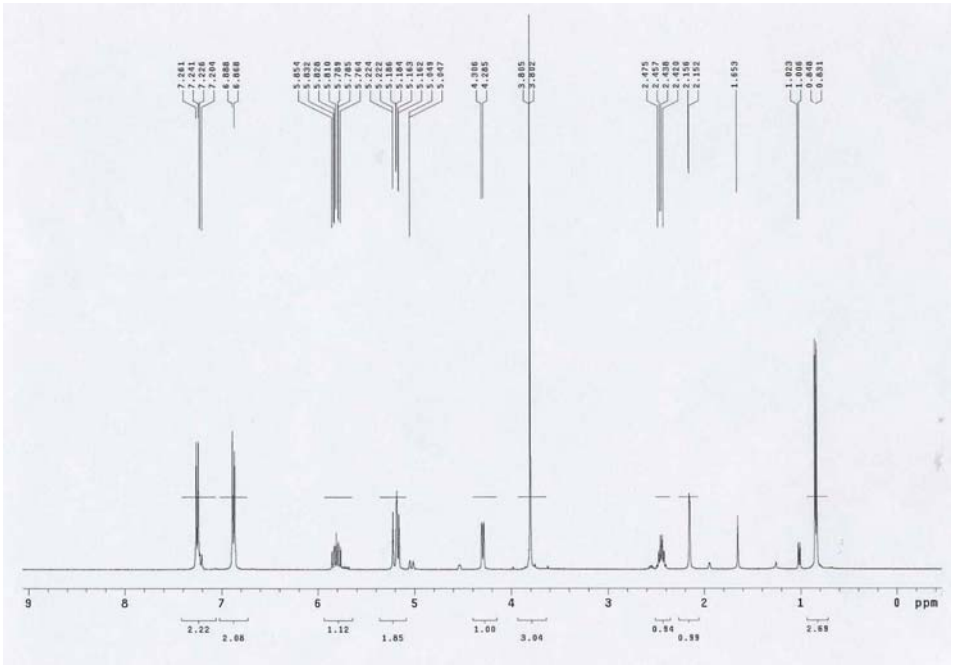
(1*S*,2*S*)-1-(4-Methoxyphenyl)-2-methylbut-3-en-1-ol



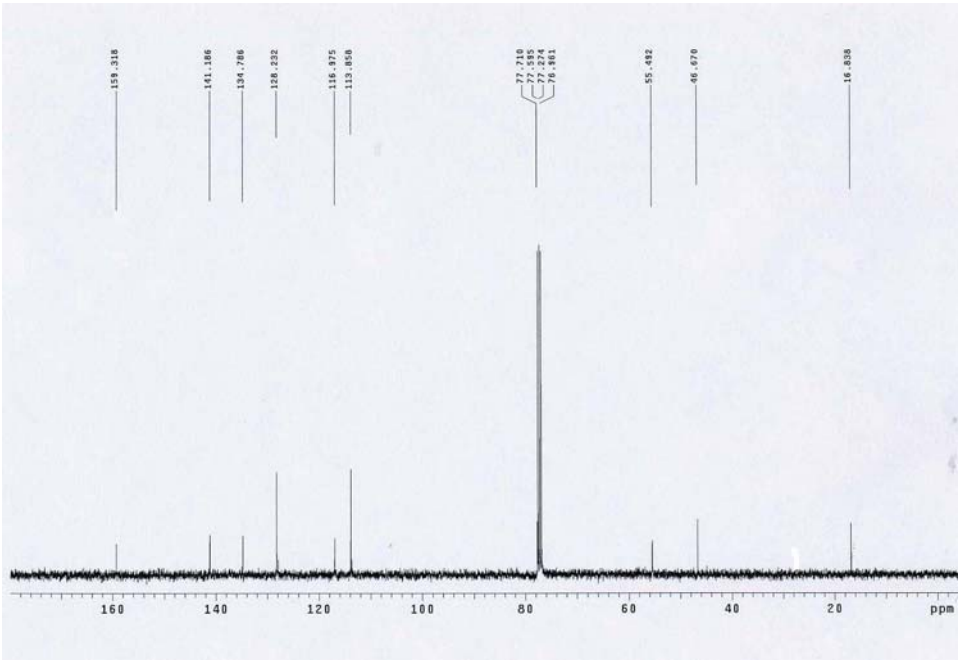
3.3c

TLC (SiO_2): R_f = 0.28 (ethyl acetate:hexanes, 1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.86-5.76 (m, 1H), 5.23-5.16 (m, 2H), 4.29 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 2.48-2.42 (m, 1H), 2.15 (br s, 1H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 141.2, 134.8, 128.2, 117.0, 113.9, 77.7, 55.5, 46.7, 16.8. HPLC: (Chiralpak AD-H/AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 230 nm), t_{minor} = 41.2 min, t_{major} = 48.9 min; ee = 90% (alcohol), 97% (aldehyde).

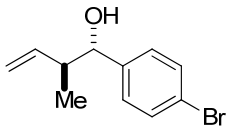
^{1}H NMR



^{13}C NMR



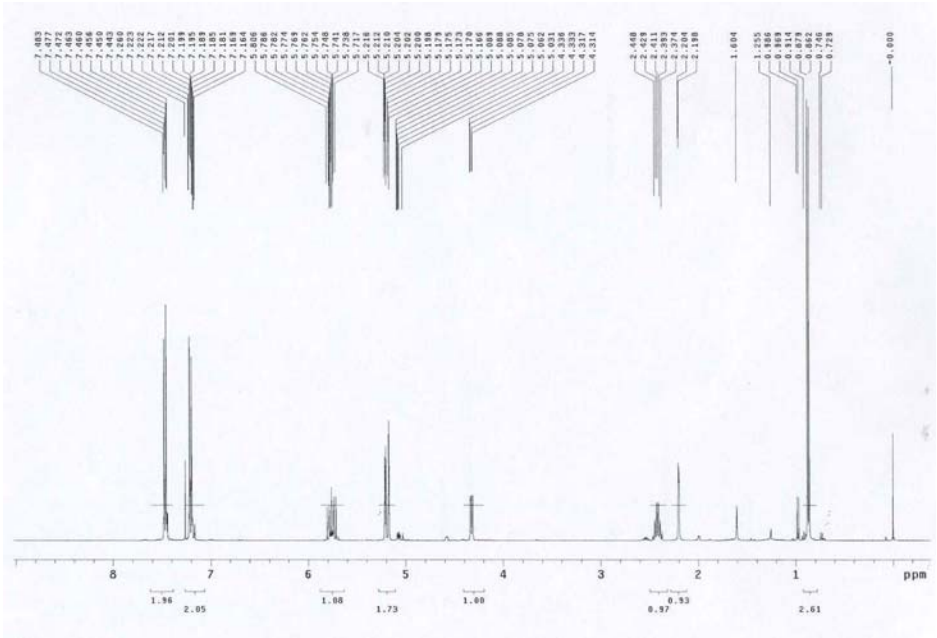
(1*S*,2*S*)-1-(4-Bromophenyl)-2-methylbut-3-en-1-ol



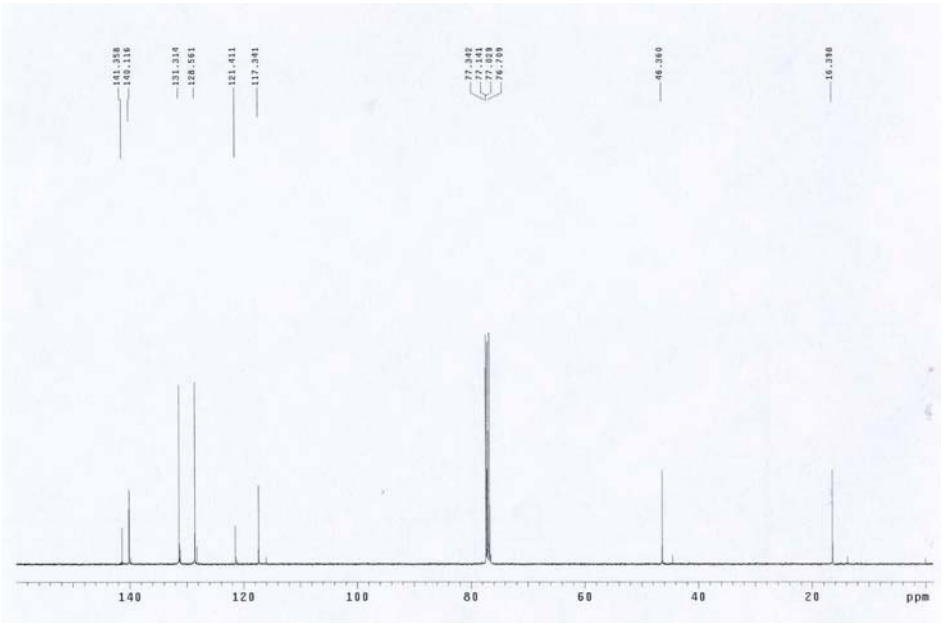
3.3d

TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.81-5.71 (m, 1H), 5.22-5.16 (m, 2H), 4.32 (d, *J* = 7.6 Hz, 1H), 2.45-2.37 (m, 1H), 2.20 (br s, 1H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 140.1, 131.3, 128.6, 121.4, 117.3, 77.1, 46.4, 16.4. HPLC: (Chiralpak AS-H/AS-H column, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm), t_{minor} = 30.0 min, t_{major} = 34.4 min; ee = 95% (alcohol), 97% (aldehyde).

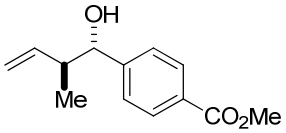
^{1}H NMR



^{13}C NMR



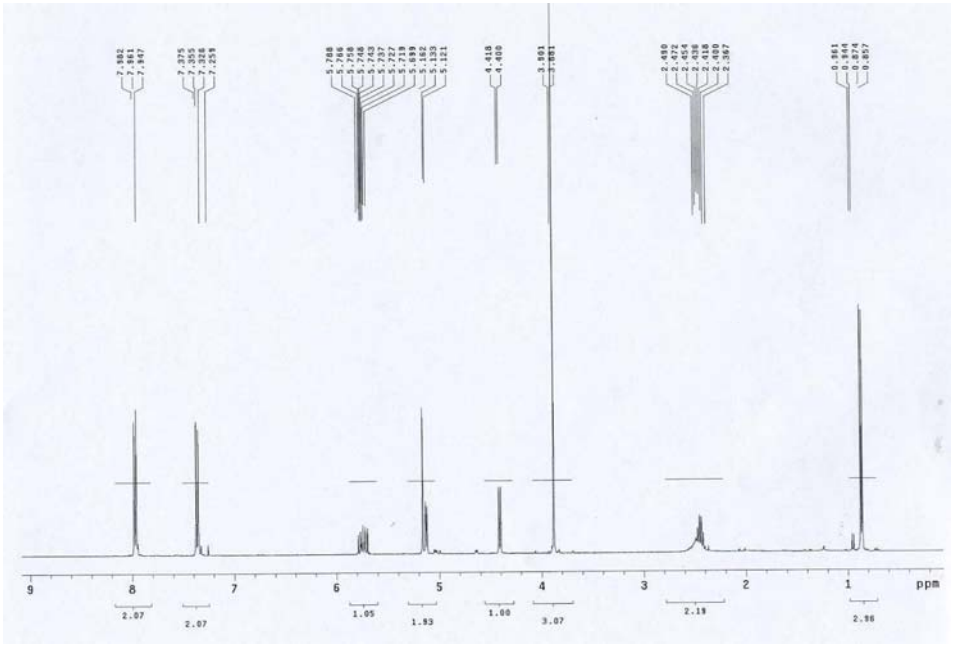
Methyl 4-((1*S*,2*S*)-1-hydroxy-2-methylbut-3-enyl)benzoate



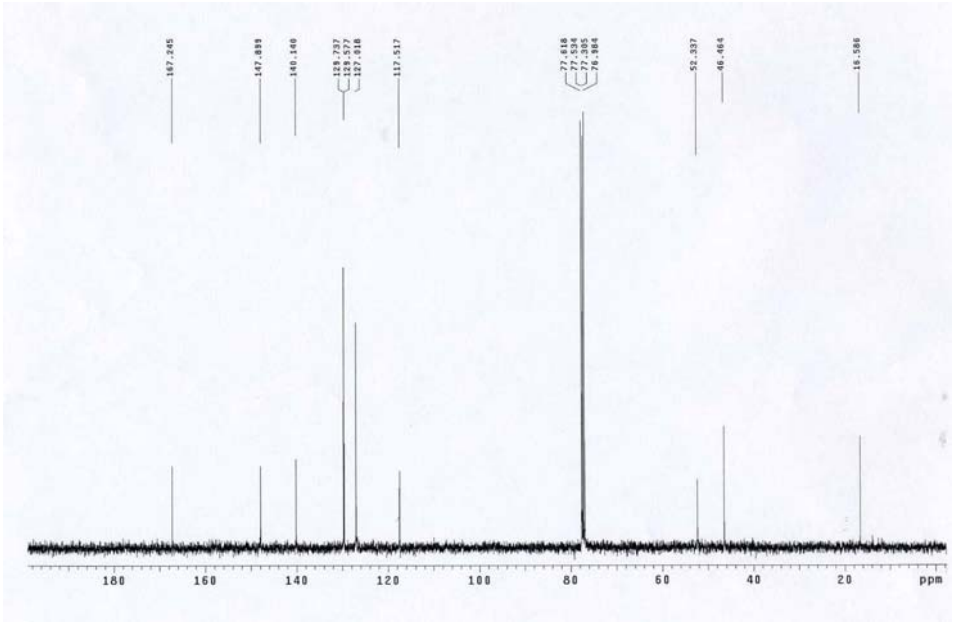
3.3e

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.79-5.69 (m, 1H), 5.17-5.12 (m, 2H), 4.40 (d, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 2.49-2.36 (m, 2H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 147.9, 140.1, 129.7, 129.6, 127.0, 117.5, 77.3, 52.3, 46.5, 16.6. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 25.3 min, t_{major} = 30.3 min; ee = 97% (alcohol), 97% (aldehyde).

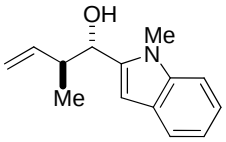
^{1}H NMR



^{13}C NMR



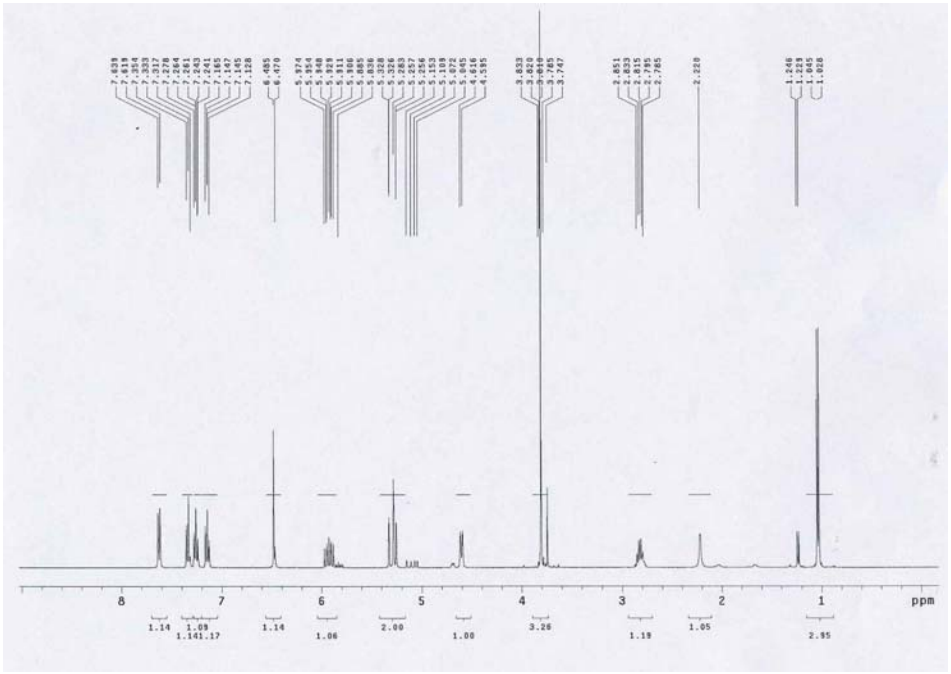
(1*S*,2*S*)-2-Methyl-1-(1-methyl-1*H*-indol-2-yl)but-3-en-1-ol



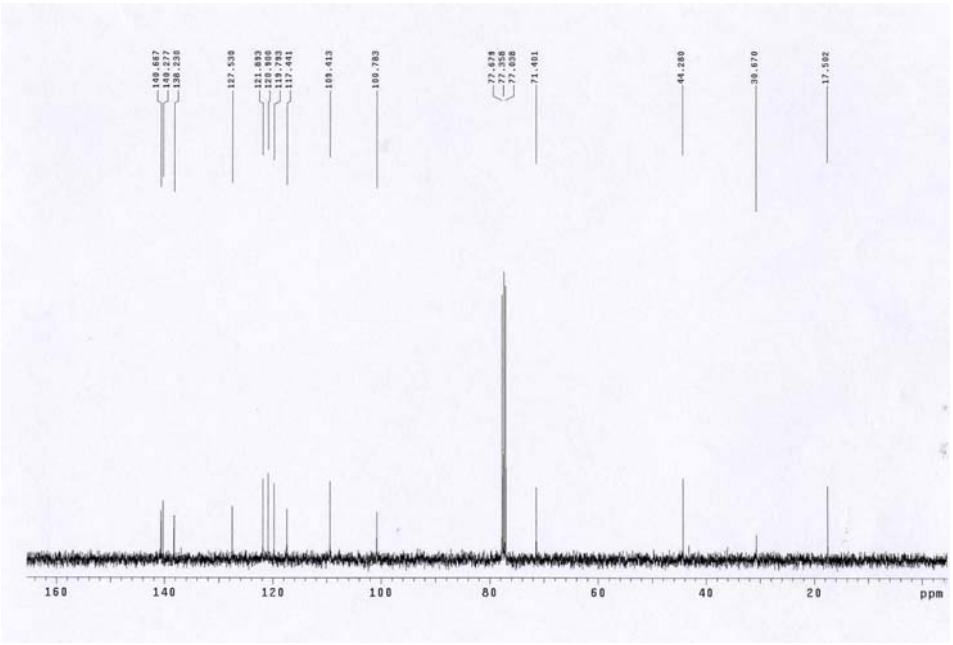
3.3f

TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 5.98-5.88 (m, 1H), 5.33-5.25 (m, 2H), 4.60 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 2.86-2.78 (m, 1H), 2.22 (br s, 1H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 140.3, 138.2, 127.5, 121.9, 120.9, 119.8, 117.4, 109.4, 100.8, 71.4, 44.3, 30.7, 17.5. FTIR (neat): υ 3512, 3415, 3052, 2972, 2929, 1638, 1611, 1540, 1468, 1416, 1316, 1233, 1138, 1102, 1010, 918, 842, 785, 750, 735, 672 cm^{-1}. HRMS (CI) Calcd. for $C_{14}H_{18}NO$ (M+1): 202.1388, Found: 202.1389. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 93:7, 0.5 mL/min, 254 nm), t_{major} = 62.8 min, t_{minor} = 78.9 min; ee = 95% (alcohol), 97% (aldehyde).

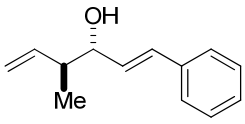
^{1}H NMR



^{13}C NMR



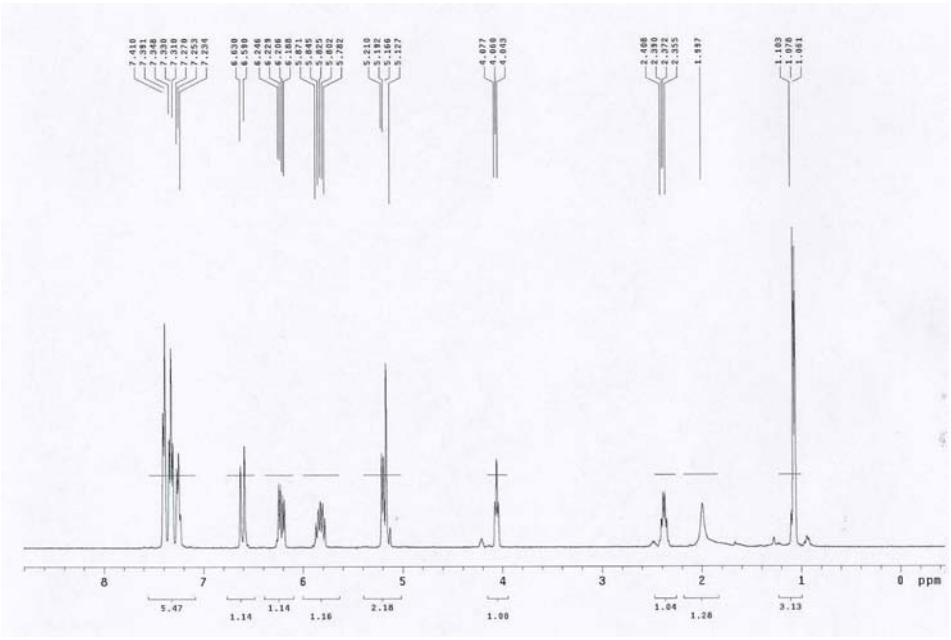
(3*R*,4*S*)-4-Methyl-1-phenylhexa-(1*E*,5)-dien-3-ol



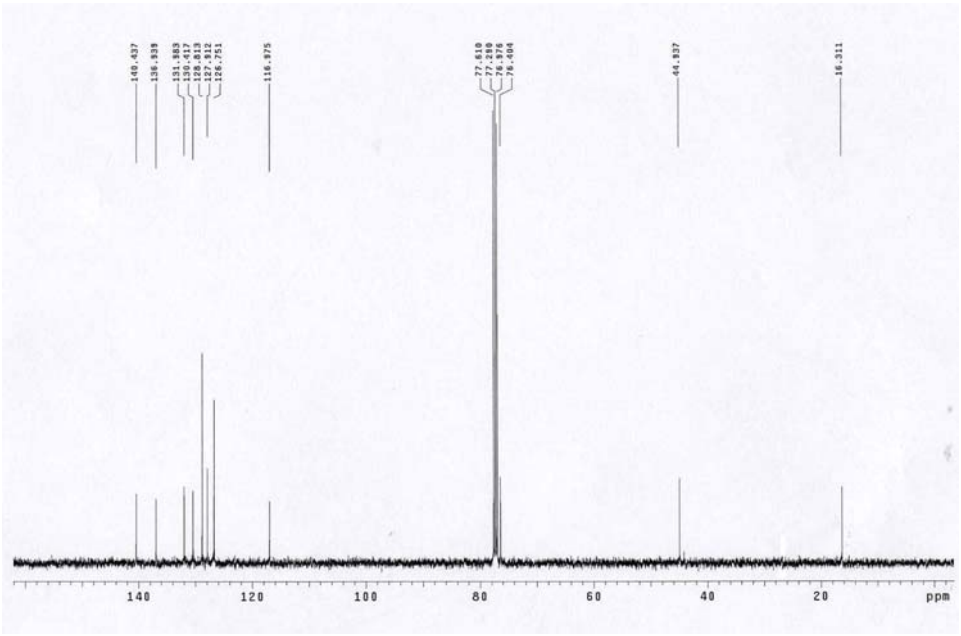
3.3g

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.23 (m, 5H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 16.0, 7.2 Hz, 1H), 5.88-5.78 (m, 1H), 5.21-5.16 (m, 2H), 4.06 (t, *J* = 6.8 Hz, 1H), 2.41-2.35 (m, 1H), 1.99 (br s, 1H), 1.06 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 136.9, 132.0, 130.4, 128.8, 127.9, 126.8, 117.0, 76.4, 44.9, 16.3. HPLC: (Chiralpak AS-H/AS-H column, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm), t_{minor} = 29.2 min, t_{major} = 35.4 min; ee = 90% (alcohol), 98% (aldehyde).

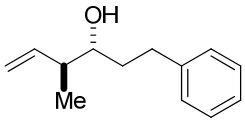
^{1}H NMR



^{13}C NMR



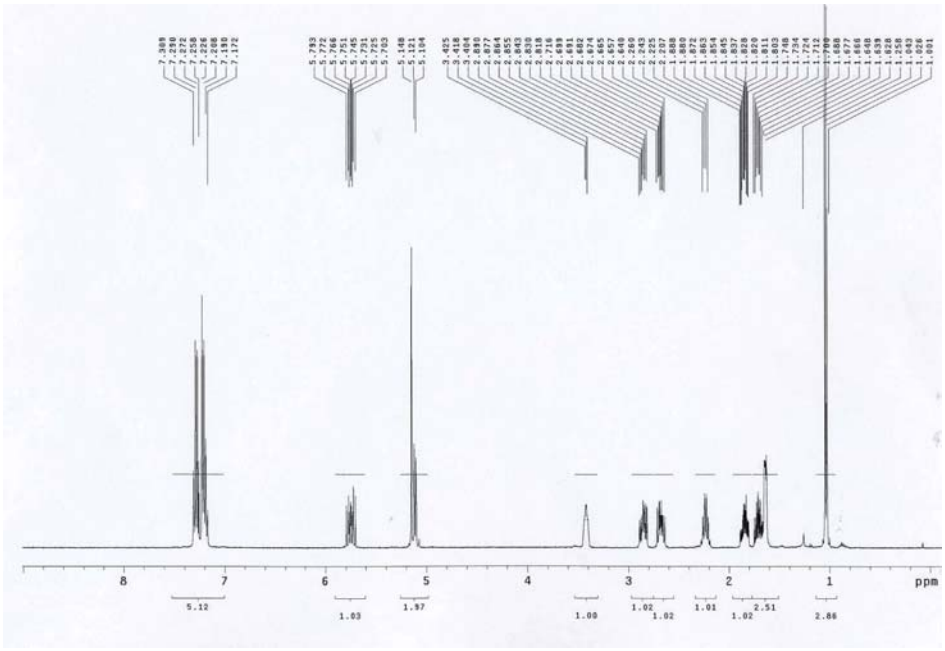
(3*R*,4*S*)-4-Methyl-1-phenylhex-5-en-3-ol



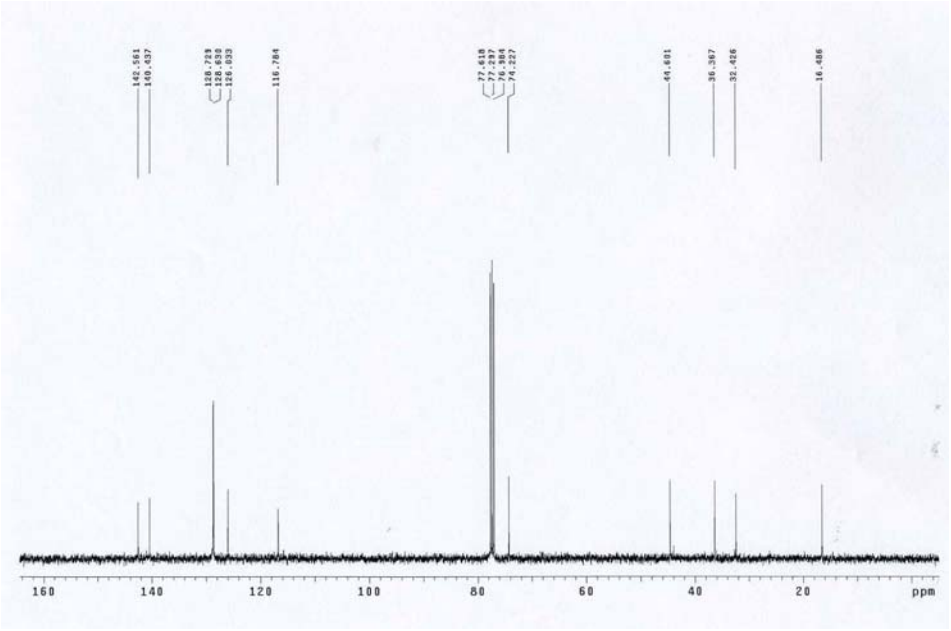
3.3h

TLC (SiO_2): R_f = 0.31 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 5.80-5.70 (m, 1H), 5.15-5.10 (m, 2H), 3.43-3.40 (m, 1H), 2.89-2.81 (m, 1H), 2.72-2.64 (m, 1H), 2.26-2.20 (m, 1H), 1.89-1.80 (m, 1H), 1.75-1.62 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.4, 128.7, 128.6, 126.0, 116.8, 74.2, 44.6, 36.4, 32.4, 16.5. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.7 mL/min, 254 nm), t_{minor} = 11.2 min, t_{major} = 17.4 min; ee = 97% (alcohol), 97% (aldehyde).

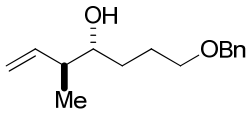
^{1}H NMR



^{13}C NMR



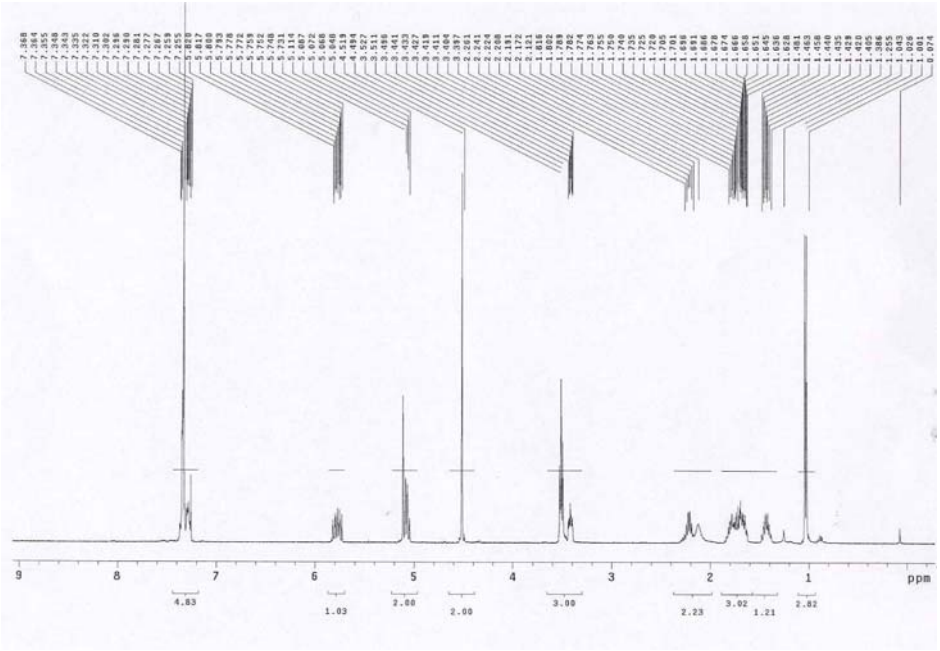
(3*S*,4*R*)-7-(Benzyloxy)-3-methylhept-1-en-4-ol



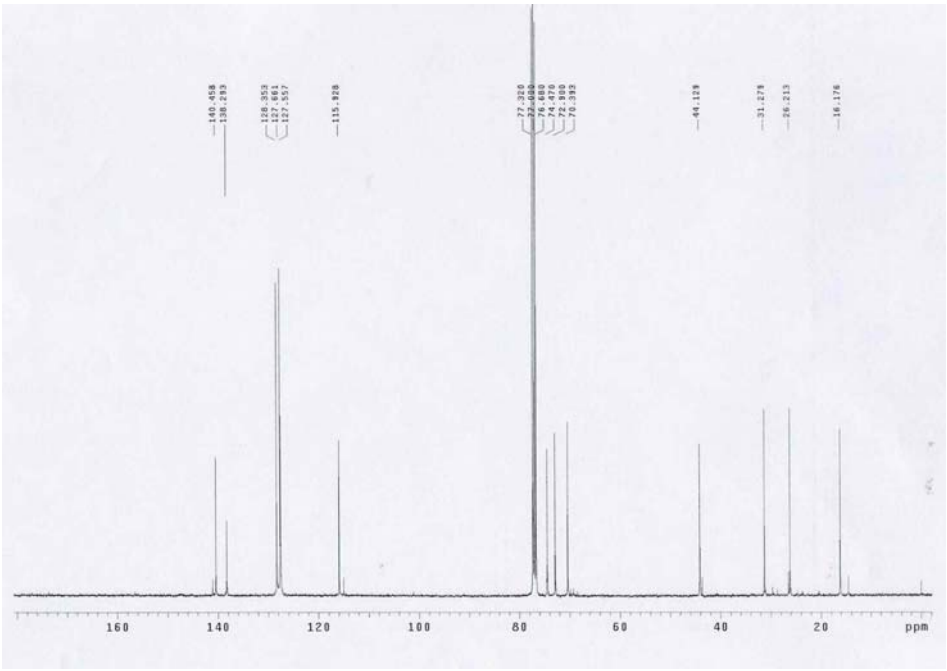
3.3i

TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:12). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 5.82-5.73 (m, 1H), 5.12-5.06 (m, 2H), 4.51 (s, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.45-3.39 (m, 1H), 2.27-2.17 (m, 1H), 2.12 (br s, 1H), 1.82-1.62 (m, 3H), 1.49-1.38 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 138.3, 128.4, 127.7, 127.6, 115.9, 74.5, 72.9, 70.4, 44.1, 31.3, 26.2, 16.2. HPLC: Enantiomeric excess was determined by HPLC analysis of the 2-naphthoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98.5:1.5, 1.0 mL/min, 230 nm), t_{major} = 16.4 min, t_{minor} = 25.8 min; ee = 97% (alcohol), 97% (aldehyde).

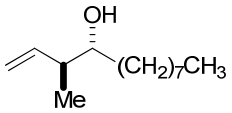
^{1}H NMR



^{13}C NMR



(3*S*,4*R*)-3-Methyldodec-1-en-4-ol

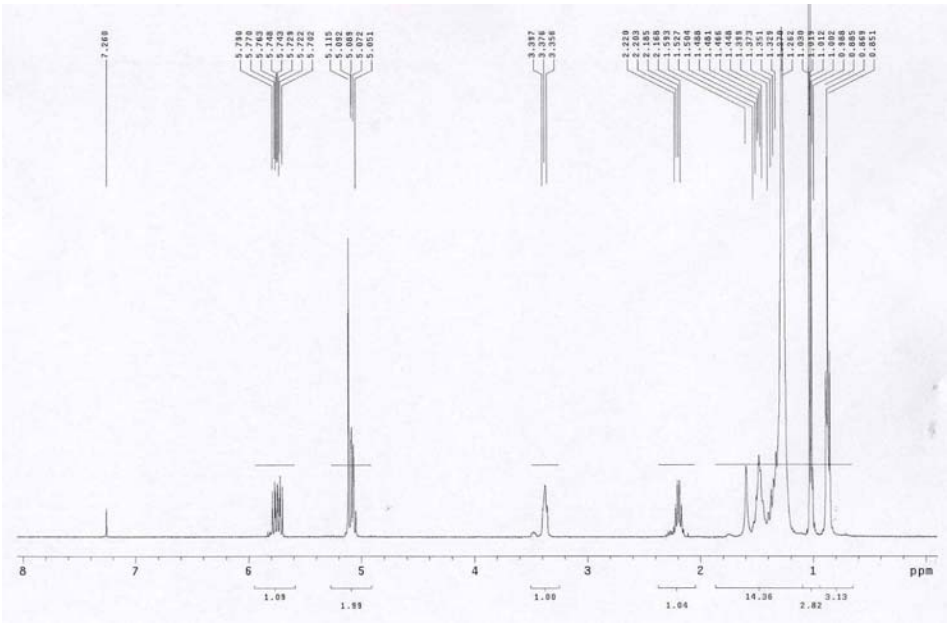


3.3j

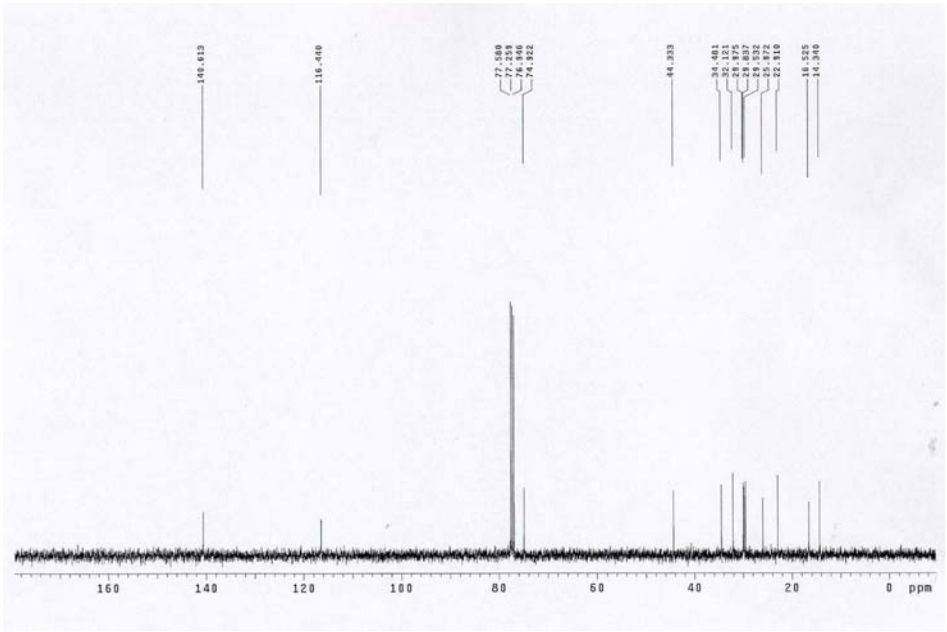
TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79-5.70 (m, 1H), 5.12-5.07 (m, 2H), 3.40-3.35 (m, 1H), 2.20-2.16 (m, 1H), 1.59 (br s, 1H), 1.53-1.26 (m, 14H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 116.4, 74.9, 44.3, 34.5, 32.1, 30.0, 29.8, 29.5, 26.0, 22.9, 16.5, 14.3. HPLC: Enantiomeric excess was determined by HPLC analysis of the 2-naphthoate derivative of the product (Chiralpak AD-H column, hexanes:*i*-PrOH = 99.5:0.5, 0.4

mL/min, 254 nm), t_{minor} = 12.9 min, t_{major} = 18.3 min; ee = 97% (alcohol), 97% (aldehyde).

^{1}H NMR

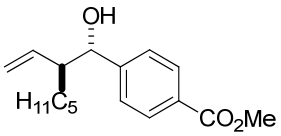


^{13}C NMR



Detailed Procedure and Spectral Data for Experiments Aimed at Probing the Origins of Stereoselection

Methyl 4-((1*S*,2*S*)-1-hydroxy-2-vinylheptyl)benzoate



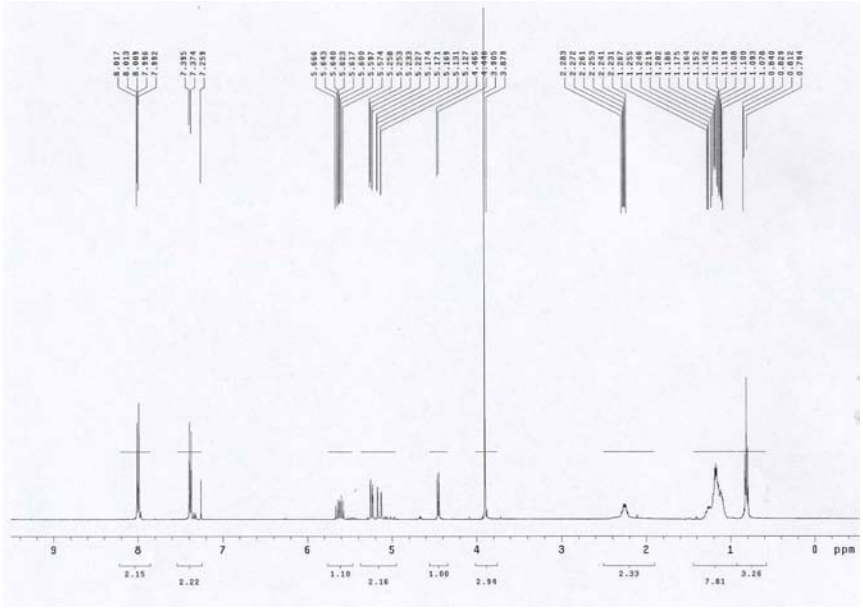
3.5

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), BIPHEP (10.5 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by (*R*)-oct-1-en-3-yl acetate (**3.4**) (136 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to room temperature. Methyl 4-(hydroxymethyl)benzoate **3.1e** (66.5 mg, 0.4 mmol, 100 mol%) in THF (0.2 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) provided **3.5** (53.1 mg, 0.192 mmol, *anti*:*syn* = 9:1) as a pale yellow oil in 48% yield.

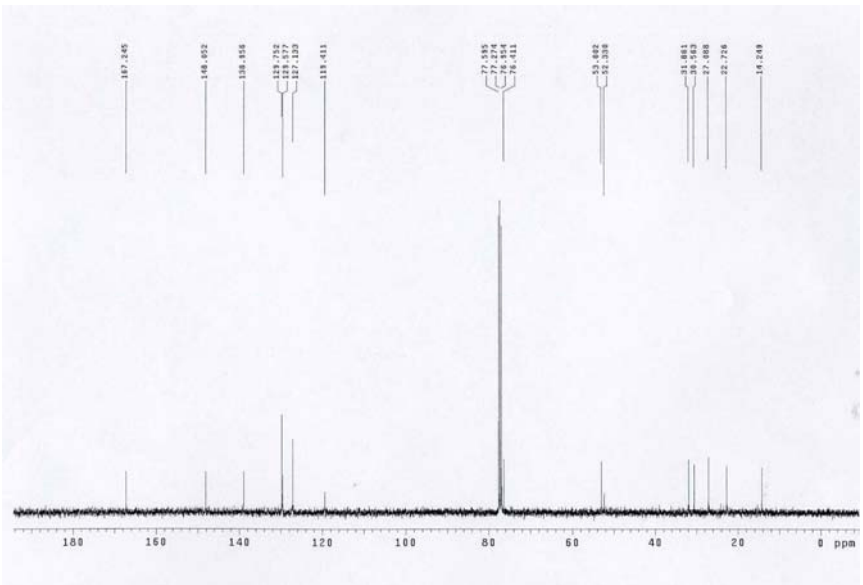
TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 5.62 (ddd, *J* = 16.0, 10.0, 7.6 Hz, 1H), 5.24 (d, *J* = 10.0, 7.6 Hz, 1H), 5.17 (dd, *J* = 16.0, 7.6 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 2.29-2.23 (m, 2H), 1.27-1.07 (m, 8H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 148.1, 139.0, 129.8, 129.6, 127.1, 119.4, 76.4, 53.0, 52.3, 31.9,

30.6, 27.1, 22.7, 14.2. FTIR (neat): υ 3481, 2953, 2928, 2857, 2161, 1979, 1722, 1638, 1611, 1576, 1435, 1416, 1275, 1191, 1176, 1109, 1050, 1018, 999, 967, 913, 859, 809, 774, 736, 721, 709, 667 cm^{-1}. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 17.2 min, t_{major} = 23.4 min; ee = 14%.

^{1}H NMR



^{13}C NMR



Matched Case

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), (S)-SEGPHOS (12.2 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by (*R*)-oct-1-en-3-yl acetate (**3.4**) (136 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to room temperature. Methyl 4-(hydroxymethyl)benzoate 1e (66.5 mg, 0.4 mmol, 100 mol%) in THF (0.2 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^oC for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:30-1:10) provided **3.5** (68.3 mg, 0.247 mmol, 62% yield, anti:syn = 11.9:1) and **3.4** (62.5 mg, 0.367 mmol, 46% recovered yield), respectively.

HPLC for **3.5**: (Chiralpak AD-H column, hexanes:i-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 16.4 min, t_{major} = 22.1 min; ee = 95%.

HPLC for **3.4**: Enantiomeric excess was determined by HPLC analysis of the 3,5-dinitrobenzoate derivative of the alcohol obtained from deacetylation of 4 (Chiralcel OJ-H column, hexanes:i-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 10.3 min, t_{minor} = 11.3 min; ee = 39%.

Mismatched Case

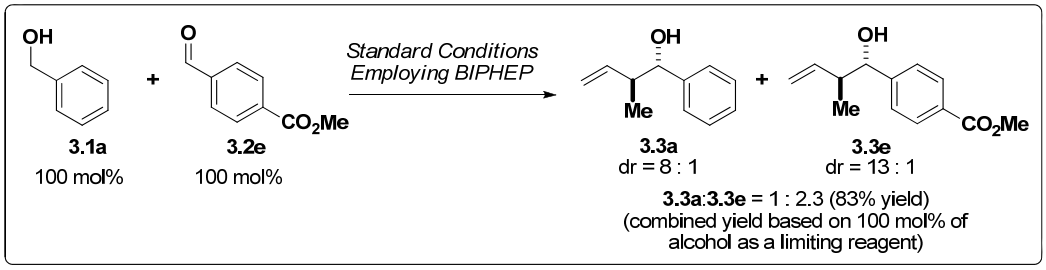
To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), (*R*)-SEGPHOS (12.2 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by (*R*)-oct-1-en-3-yl acetate[9] (**3.4**) (136 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to room temperature. Methyl 4-(hydroxymethyl)benzoate **1e** (66.5 mg, 0.4 mmol, 100 mol%) in THF (0.2 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^oC for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:30-1:10) provided ***ent*-3.5** (37.8 mg, 0.137 mmol, 34% yield, *anti*:*syn* = 4.6:1) and **3.4** (80.3 mg, 0.472 mmol, 59% recovered yield), respectively.

HPLC for *ent*-5: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{major} = 17.6 min, t_{minor} = 21.8 min; ee = 73%.

HPLC for 4: Enantiomeric excess was determined by HPLC analysis of the 3,5-dinitrobenzoate derivative of the alcohol obtained from deacetylation of 4 (Chiralcel OJ-H column, hexanes:*i*-PrOH = 99:1, 1.0 mL/min, 254 nm), t_{major} = 10.0 min, t_{minor} = 11.0 min; ee = 30%.

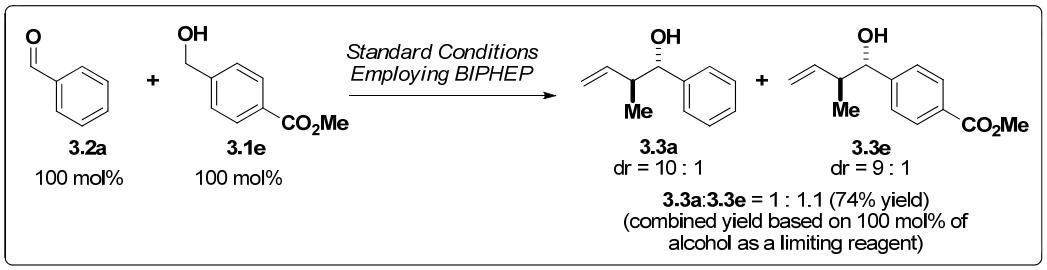
Competition Experiment Establishing Rapid Redox Equilibration

Reaction between Alcohol (3.1a) and Aldehyde (3.2e)



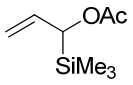
To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), BIPHEP (10.5 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by acetic acid 3-buten-2-yl ester (91.3 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to room temperature. Benzyl alcohol **3.1a** (43.3 mg, 0.4 mmol, 100 mol%) and methyl 4-formylbenzoate **3.2e** (65.7 mg, 0.4 mmol, 100 mol%) in THF (0.2 mL) were added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^oC for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20-1:10) provided 3a (22.1 mg, 0.136 mmol, 34% yield, *anti*:*syn* = 8:1) and **3.3e** (42.8 mg, 0.194 mmol, 49% yield, *anti*:*syn* = 13:1).

Reaction between Aldehyde (3.2a) and Alcohol (3.1e)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2.5 mol%), BIPHEP (10.5 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (26.1 mg, 0.08 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 10 mol%) was added THF (0.2 mL) followed by acetic acid 3-buten-2-yl ester (91.3 mg, 0.8 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to room temperature. Benzaldehyde **3.2a** (42.4 mg, 0.4 mmol, 100 mol%) and methyl 4-(hydroxymethyl)benzoate **3.1e** (66.5 mg, 0.4 mmol, 100 mol%) in THF (0.2 mL) were added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^oC for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20-1:10) provided **3.3a** (22.7 mg, 0.140 mmol, 35% yield, *anti*:*syn* = 10:1) and 3e (34.1 mg, 0.155 mmol, 39% yield, *anti*:*syn* = 9:1).

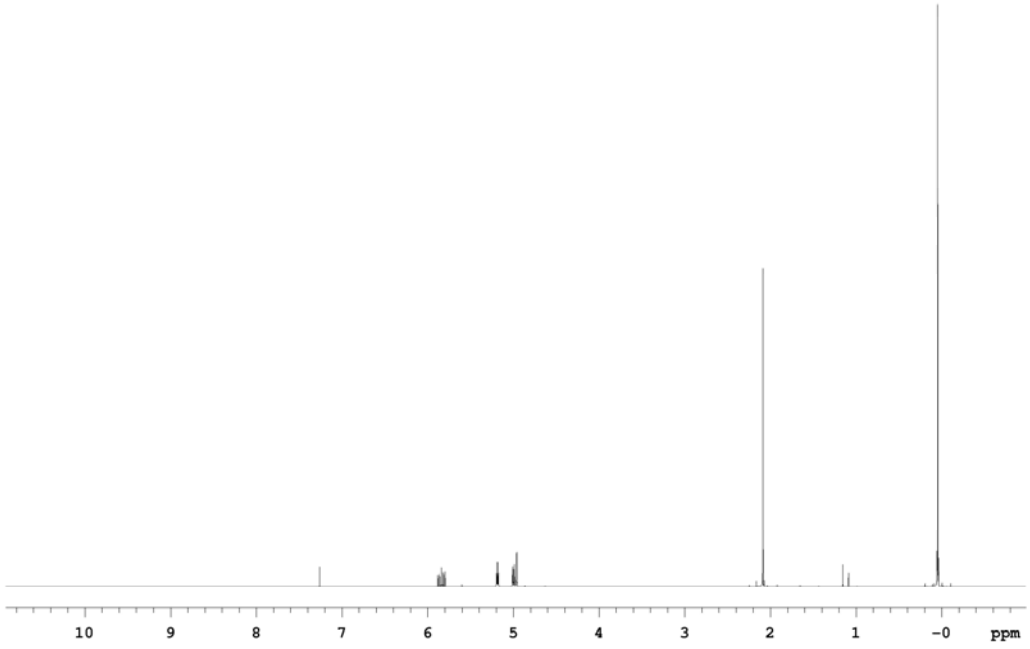
1-(trimethylsilyl)allyl acetate



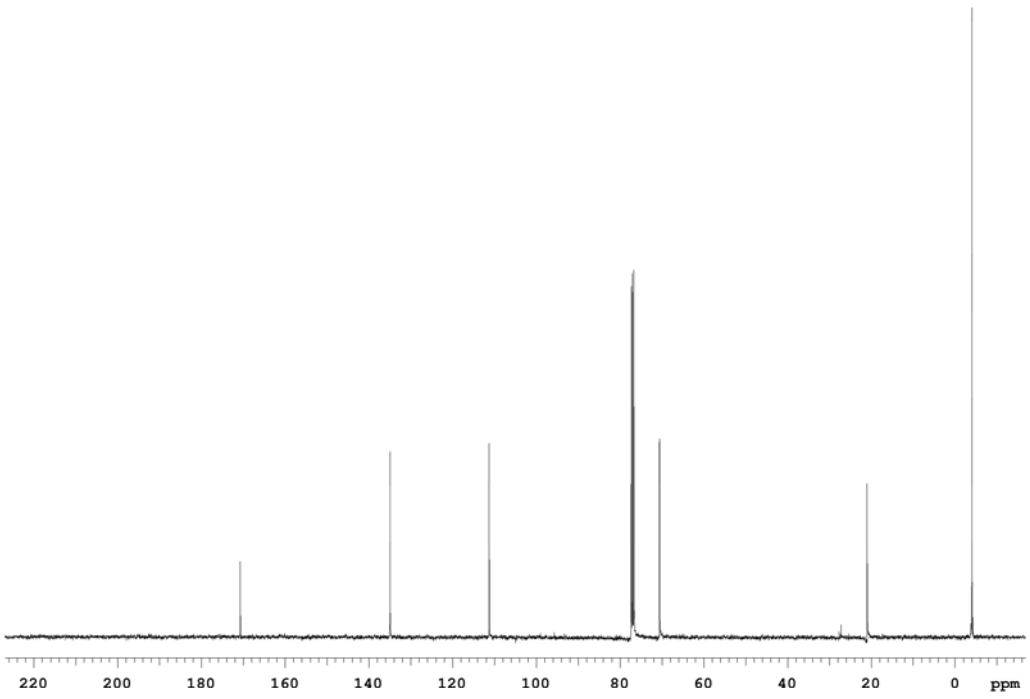
Trirmethylsilyl allyl ether (10.0 g, 0.076 mol, 100 mol%) was dissolved in THF (250 mL, 0.3 M), and then cooled to -78 ^{o}C. 1.7 M solution of *t*-butyllithium in pentane (51 mL, 0.087 mol, 115 mol%) was added dropwise over 15 min and the resulting bright yellow solution was stirred for 2 hr at -78 ^{o}C. The reaction mixture was quenched with acetic anhydride (8.025 g, 0.079 mol, 105 mol%) at -78 ^{o}C and then stirred at ambient temperature overnight. Thre resulting mixture was diluted with water (50 mL) and pentane (100 mL). The organic phase was separated and washed with water (3 times) and brine. The resulting solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; Pentane: Ether, 20:1) provied 1a (9.2 g, 0.053 mmol) as a pale yellow oil in 70% yield.

TLC (SiO_2): R_f = 0.6 (ethyl acetate: hexanes, 1:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.80 (m, 1H), 5.18 (dt, *J* = 5.6, 2.0 Hz, 1H), 5.00 (dt, *J* = 8.4, 2.0 Hz, 1H), 4.97-4.95 (m, 1H), 2.09 (s, 3H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 134.9, 111.2, 70.5, 21.0, -4.1. FTIR (neat): υ 2960, 1739, 1634, 1408, 1369, 1230, 1159, 1086, 1017, 991, 901, 839, 785, 752, 722, 696.

^{1}H NMR



^{13}C NMR



Preparation of (*R*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*R*)-SEGPHOS (159 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL), then hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (101 mg, 0.098 mmol, 75% yield).

Preparation of (*R*)-C3-TUNEPHOS

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*R*)-C3-TUNEPHOS (155 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL), then hexanes (50 mL)

was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (103 mg, 0.101 mmol, 78% yield).

General procedure for *anti*-Diastereo- and Enantioselective Carbonyl (Trimethylsilyl)allylation from the Alcohol Oxidation Level

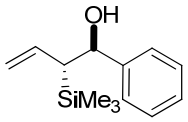
An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with alcohol (0.20 mmol, 100 mol%), ***(R)*-I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^{o}C for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column the corresponding product.

General procedure for *anti*-Diastereo- and Enantioselective Carbonyl (Trimethylsilyl)allylation from the Aldehyde Oxidation Level

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with aldehyde (0.20 mmol, 100 mol%), ***(R)*-I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^{o}C for 48 hr, at

which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography provided the corresponding product.

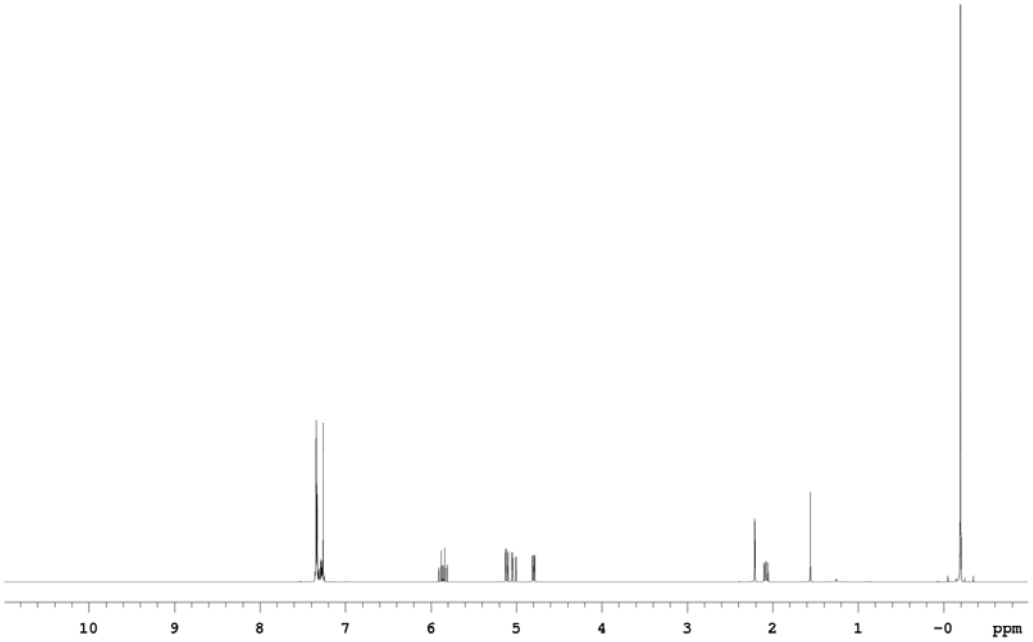
(1*S*,2*R*)-1-phenyl-2-(trimethylsilyl)but-3-en-1-ol



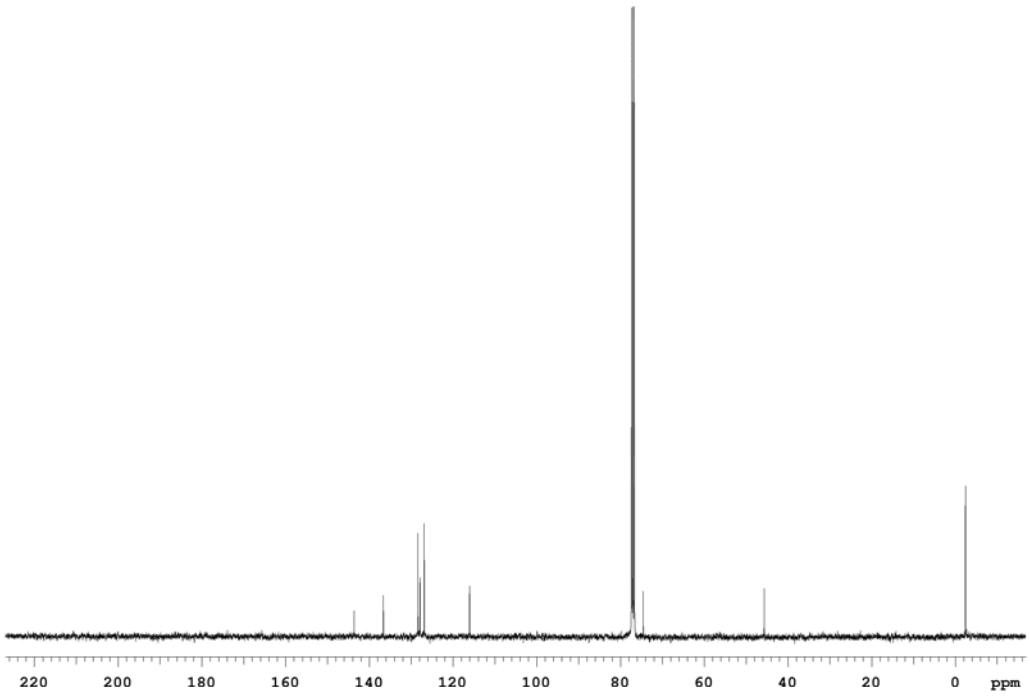
3.5a

TLC (SiO_2): R_f = 0.3 (ethyl acetate: hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 5.86 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.11 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.05-5.00 (m, 1H), 4.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.21 (d, *J* = 1.6 Hz, 1H), 2.10-2.05 (m, 1H), -0.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 136.6, 128.4, 127.8, 126.9, 116.0, 74.5, 45.6, -2.4. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 11.0 min, t_{major} = 11.6 min; ee = 96% (alchol), 96% (aldehyde). $[\alpha]_D^{25}$= +47.01 (c =2.8, $CHCl_3$). To corroborate the assignement of absolute stereochemistry, the optical rotation was correlated with a known compound (A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc*. **1992**, *114*, 2321.). FTIR (neat): υ 3426, 2953, 2896, 1626, 1494, 1455, 1386, 1247, 1196, 1153, 1089, 1050, 1028, 988, 906, 835, 786, 763, 718, 698 cm^{-1}. HRMS (CI) Calcd. for $C_{13}H_{21}OSi$ $[M+H]^+$: 221.1362, Found: 221.1356.

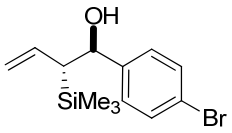
^{1}H NMR



^{13}C NMR



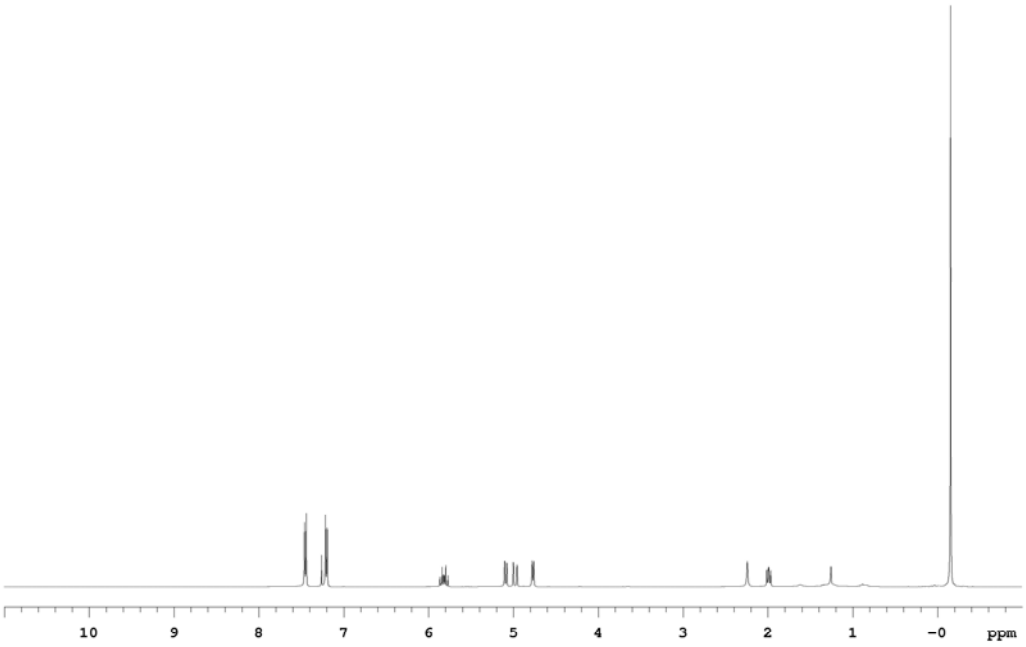
(1*S*,2*R*)-1-(4-bromophenyl)-2-(trimethylsilyl)but-3-en-1-ol



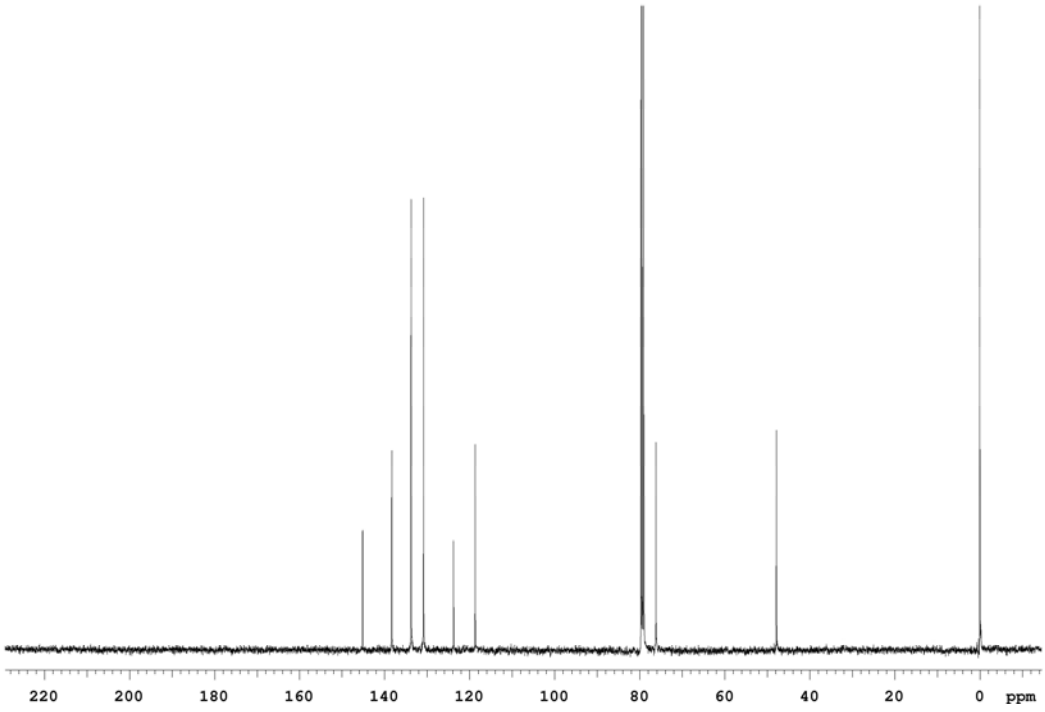
3.5b

TLC (SiO_2): R_f = 0.3 (ethyl acetate: hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4, 2H), 7.46 (d, *J* = 8.4, 2H), 5.82 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.78 (d, *J* = 7.6 Hz, 1H), 2.20 (br, 1H), 2.02-1.97 (m, 1H), -0.16 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 135.9, 131.4, 128.5, 121.4, 116.3, 73.8, 45.5, -2.6.HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 11.9 min, t_{major} = 12.9 min; ee = 96% (alcohol), 98% (aldehyde). $[\alpha]_D^{25}$= +37.4 (c =0.62, CH_2Cl_2). FTIR (neat): υ 3430, 2953, 1625, 1592, 1485, 1408, 1247, 1191, 1155, 1088, 1070, 1010, 908, 833, 785, 753, 737, 691 cm^{-1}. HRMS (CI) Calcd. for $C_{13}H_{20}BrOSi$ $[M+H]^+$: 299.0467, Found: 209.0470.

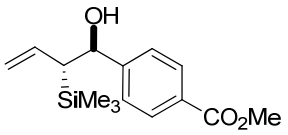
^{1}H NMR



^{13}C NMR



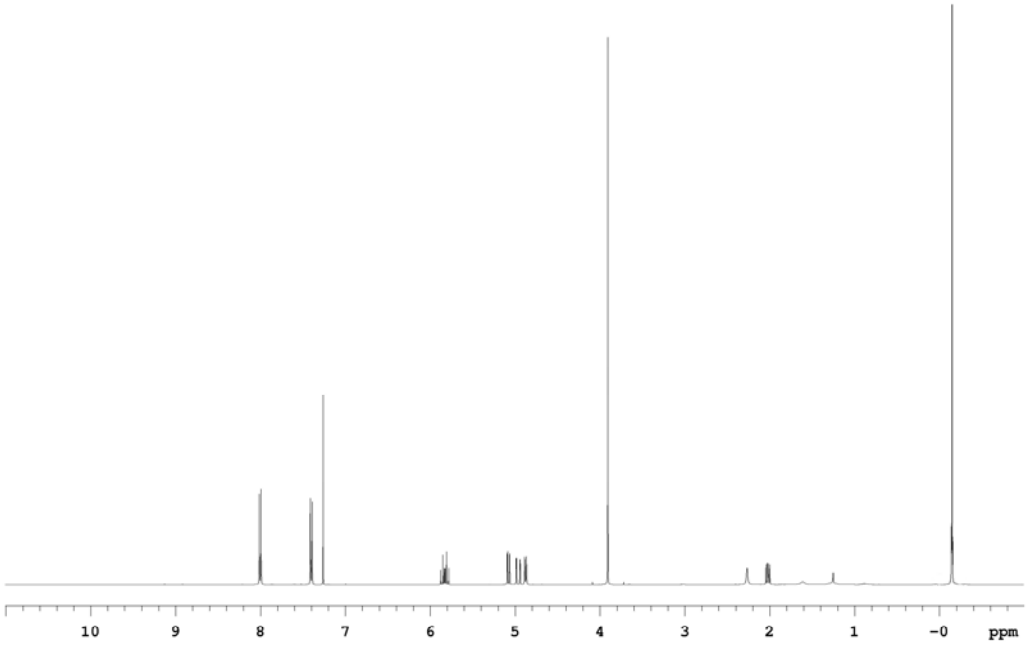
Methyl 4-((1*S*,2*R*)-1-hydroxy-2-(trimethylsilyl)but-3-enyl)benzoate



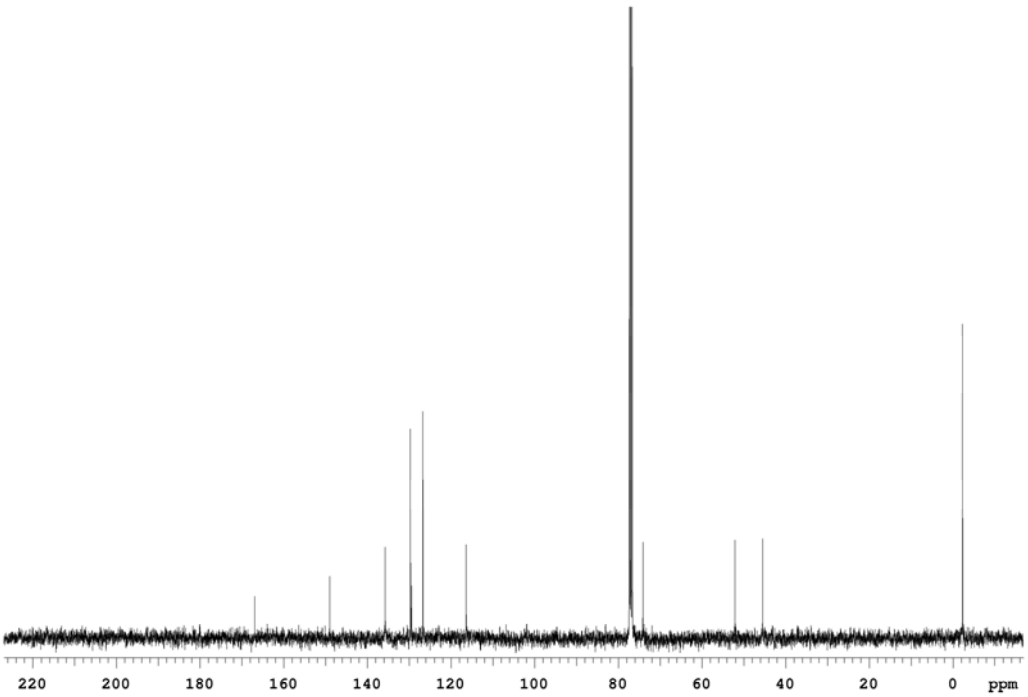
3.5c

TLC (SiO_2): R_f = 0.2 (ethyl acetate: hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.99 (m, 2H), 7.41-7.39 (m, 2H), 5.83 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.08 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.99-4.94 (m, 1H), 4.88 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 2.27 (br, 1H), 2.04-2.00 (m, 1H), -0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 149.0, 135.7, 129.7, 129.4, 126.7, 116.4, 74.1, 52.1, 45.5, -2.4. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{minor} = 12.7 min, t_{major} = 14.3 min; ee = 98% (alcohol), 98% (aldehyde). $[\alpha]_D^{25}$= +16.1 (c =0.23, CH_2Cl_2). FTIR (neat): υ 3501, 2954, 2889, 1698, 1624, 1609, 1433, 1390, 1346, 1307, 1155, 1018, 1005, 977, 955, 895, 835, 784, 772, 729, 702 cm^{-1}. HRMS (CI) Calcd. for $C_{15}H_{23}O_3Si$ $[M+H]^+$: 279.1416, Found: 279.1417.

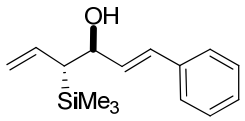
^{1}H NMR



^{13}C NMR



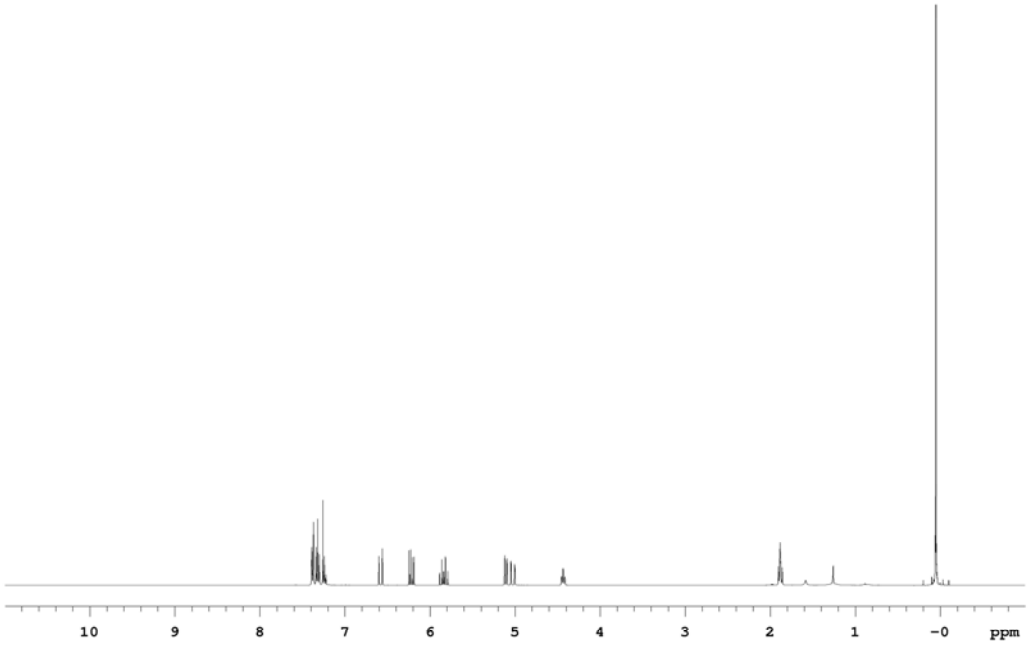
(3*S*,4*R*,*E*)-1-phenyl-4-(trimethylsilyl)hexa-1,5-dien-3-ol



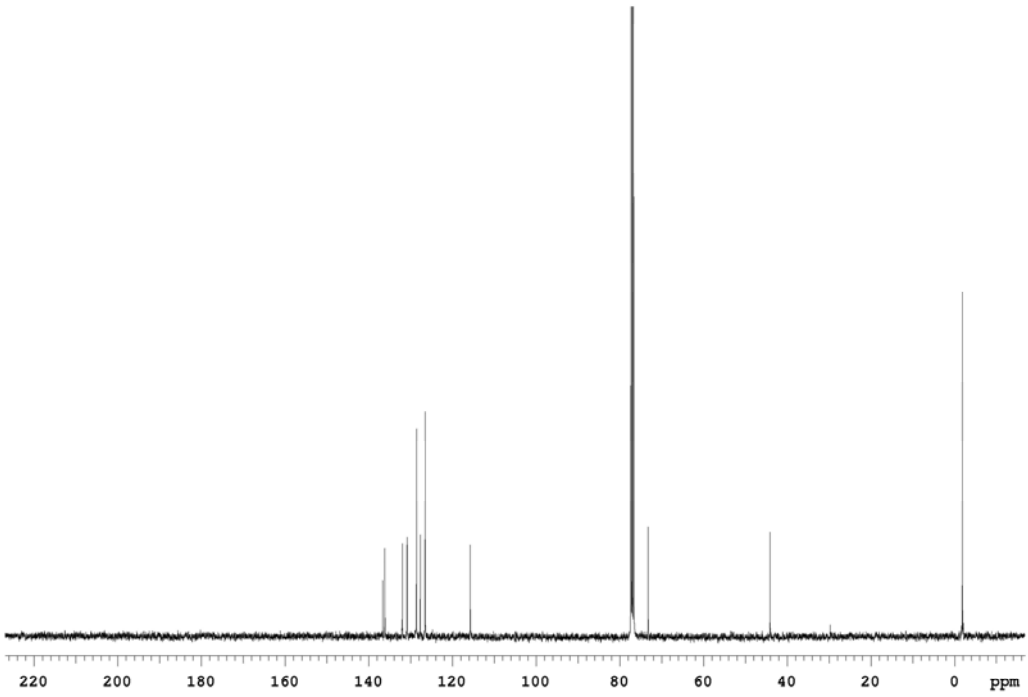
3.5d

TLC (SiO_2): R_f = 0.2 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.22 (m, 5H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.22 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.84 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.10 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.02 (ddd, *J* = 16.8, 2.0, 0.8 Hz, 1H), 4.43 (td, *J* = 7.6, 1.2 Hz, 1H), 1.90-1.86 (m, 2H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 136.1, 131.9, 130.8, 128.6, 127.7, 126.5, 115.7, 73.2, 44.1, -1.9. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 13.6 min, t_{major} = 14.8 min; ee = 92% (alcohol), 94% (aldehyde). $[\alpha]_D^{25}$= +38.8 (c =0.21, CH_2Cl_2). FTIR (neat): υ 3428, 3026, 2954, 1625, 1494, 1449, 1379, 1246, 1105, 1035, 1003, 964, 897, 860, 853, 784, 748, 724, 691 cm^{-1}. HRMS (CI) Calcd. for $C_{15}H_{23}OSi$ $[M+H]^+$: 247.1518, Found: 247.1520.

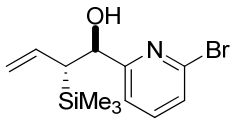
^{1}H NMR



^{13}C NMR



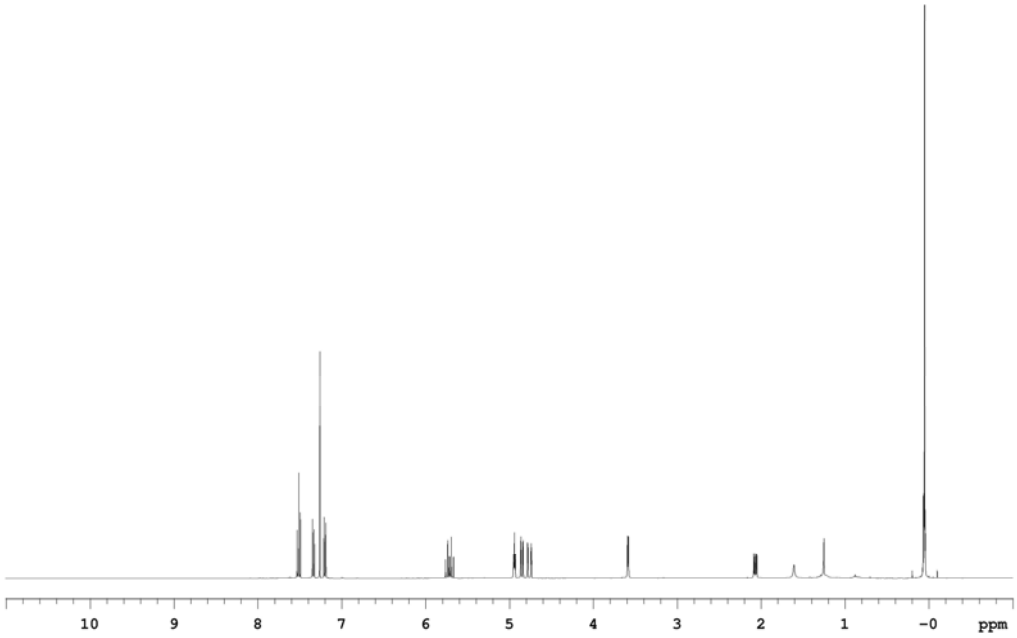
(1*S*,2*R*)-1-(6-bromopyridin-2-yl)-2-(trimethylsilyl)but-3-en-1-ol



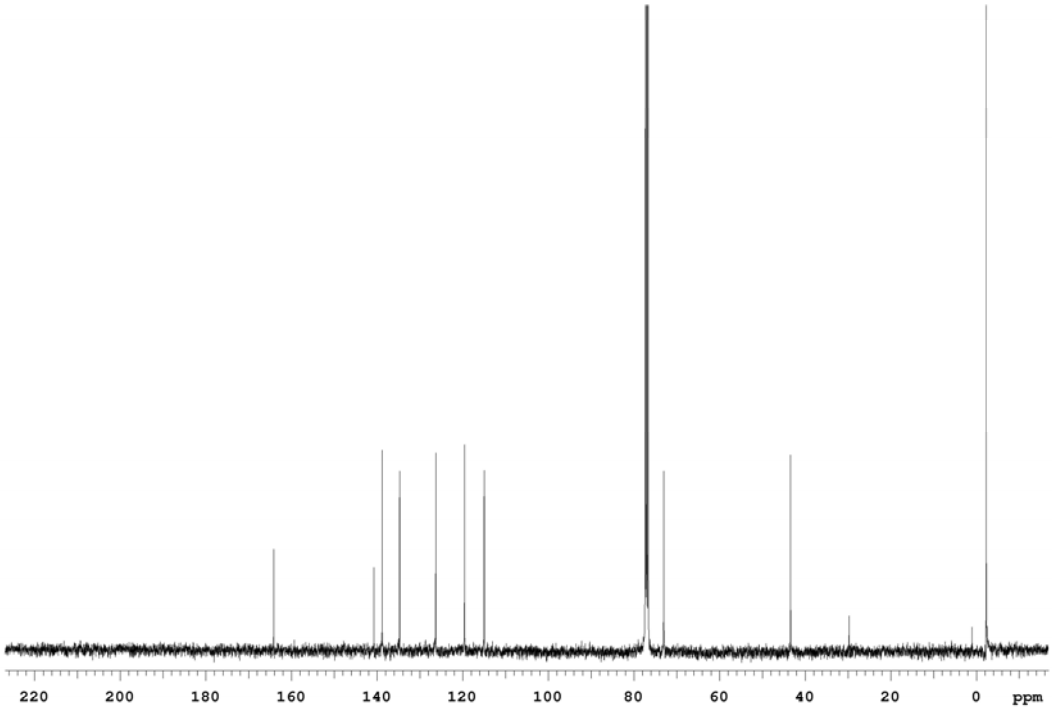
3.5e

TLC (SiO_2): R_f = 0.2 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.20 (dt, *J* = 7.6, 0.4 Hz, 1H), 5.71 (dt, *J* = 17.2, 10.4 Hz, 1H), 4.94 (t, *J* = 4.4 Hz, 1H), 4.85 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.76 (ddd, *J* = 17.2, 2.4, 0.8 Hz, 1H), 3.59 (d, *J* = 4.4 Hz, 1H), 2.07 (dd, *J* = 10.4, 4.4 Hz, 1H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 140.7, 138.8, 134.7, 126.3, 119.6, 114.9, 73.0, 43.4, -2.3. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 254 nm), t_{major} = 6.6 min , t_{minor} = 7.9 min; ee = 99% (alcohol), 99% (aldehyde). $[\alpha]_D^{25}$= -44.6 (c =0.40, CH_2Cl_2). FTIR (neat): υ 3348, 2922, 1583, 1556, 1441, 1406, 1377, 1286, 1241, 1163, 1212, 1080, 1057, 999, 930, 903, 838, 806, 779, 748, 677. HRMS (CI) Calcd. for $C_{12}H_{19}NOBrSi$ $[M+H]^+$: 300.0419, Found: 300.0424.

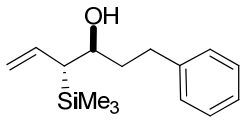
^{1}H NMR



^{13}C NMR



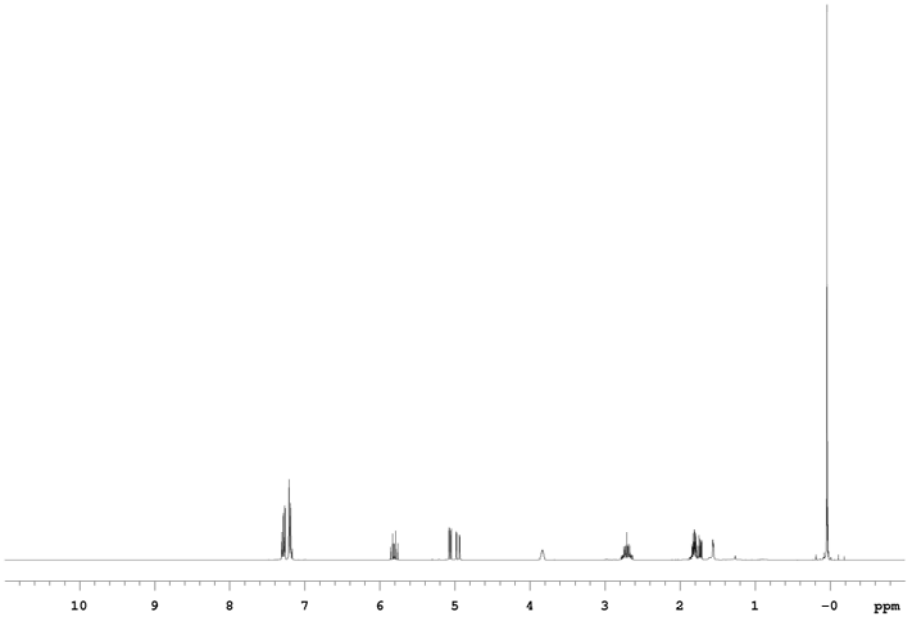
(3*S*,4*R*)-1-phenyl-4-(trimethylsilyl)hex-5-en-3-ol



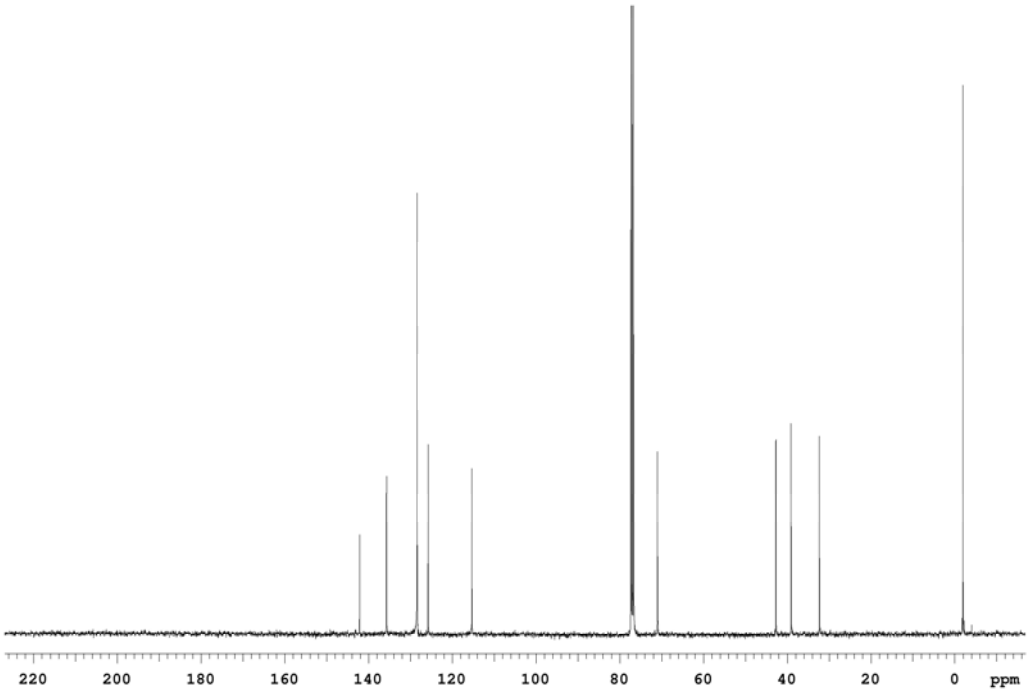
3.5f

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 5.79 (dt, *J* = 17.2, 10.8 Hz, 1H), 5.06 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.95 (dd, *J* = 17.2, 2.0 Hz, 1H), 3.84-3.82 (m, 1H), 2.76-2.63 (m, 2H), 1.84-1.71 (m, 3H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 135.7, 128.4, 128.3, 125.8, 115.3, 71.0, 42.7, 39.1, 32.3, -2.0. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 12.1 min, t_{minor} = 16.8 min ; ee = 97% (alcohol), 98% (aldehyde). $[\alpha]_D^{25}$= +13.3 (c =0.60, CH_2Cl_2). FTIR (neat): υ 3448, 3027, 2951, 1624, 1603, 1495, 1454, 1414, 1246, 1167, 1098, 1044, 999, 897, 835, 748, 698. HRMS (CI) Calcd. for $C_{15}H_{23}OSi$ $[M-H]^+$: 247.1518, Found: 247.1520.

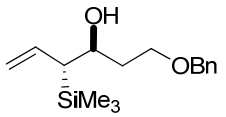
^{1}H NMR



^{13}C NMR



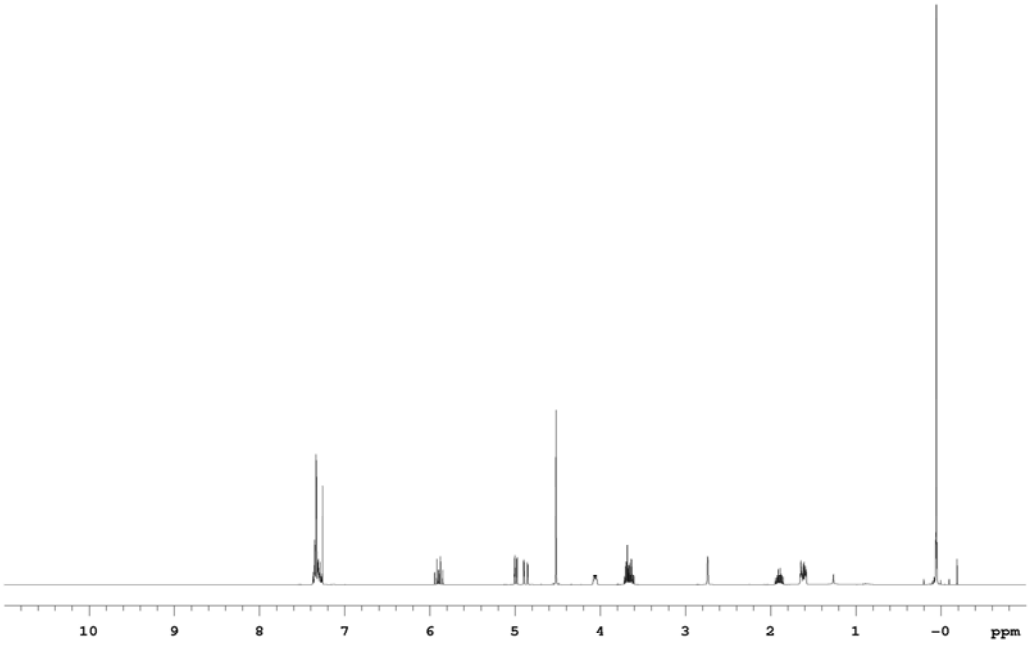
(3*S*,4*R*)-1-(benzyloxy)-4-(trimethylsilyl)hex-5-en-3-ol



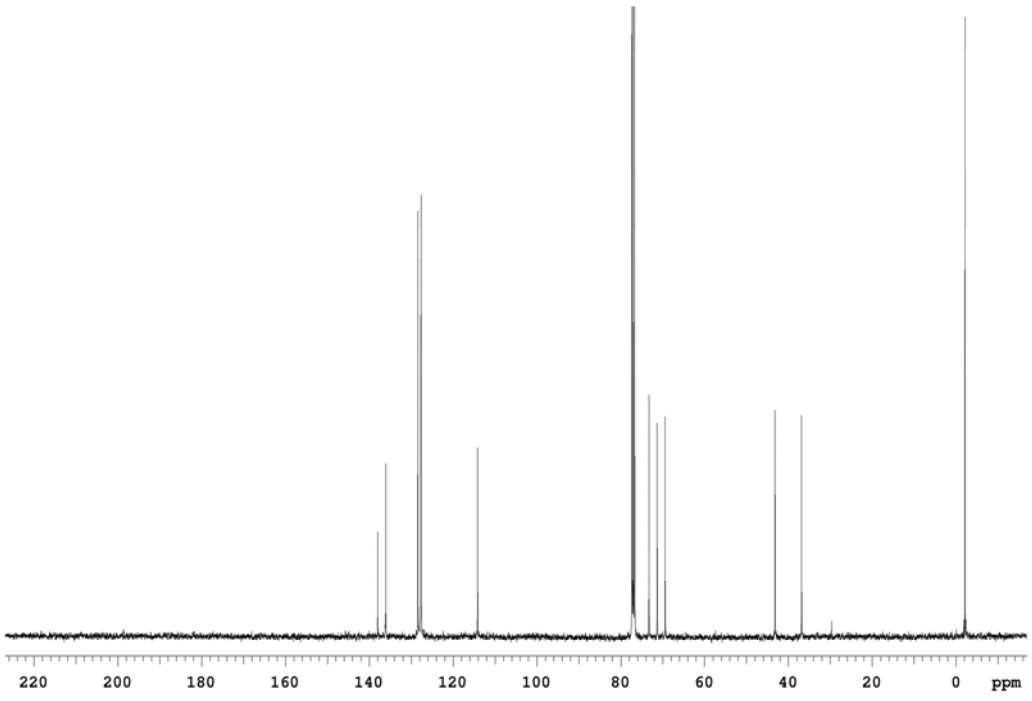
3.5g

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 5.90 (dt, *J* = 17.2, 10.4 Hz, 1H), 4.99 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.87 (ddd, *J* = 17.2, 2.4, 0.8 Hz, 1H), 4.52 (s, 2H), 4.08-4.01 (m, 1H), 3.72-3.61 (m, 2H), 2.74-2.73 (m, 1H), 1.95-1.85 (m, 1H), 1.65-1.58 (m, 2H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.1, 128.4, 127.7, 127.6, 114.1, 73.2, 71.3, 69.4, 43.2, 36.8, -2.1. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 97.5:2.5, 0.5 mL/min, 210 nm), t_{major} = 11.8 min, t_{minor} = 13.3 min; ee = 97% (alcohol), 98% (aldehyde). $[\alpha]_D^{25}$= +26.7 (c =0.64, CH_2Cl_2). FTIR (neat): υ 3511, 2951, 2860, 1623,1496, 1454, 1414, 1362, 1244, 1205, 1088, 1027, 1004, 896, 835, 780, 733, 696. HRMS (CI) Calcd. for $C_{16}H_{25}O_2Si$ $[M-H]^+$: 277.1624, Found: 277.1627.

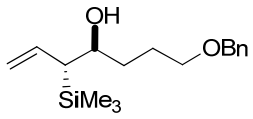
^{1}H NMR



^{13}C NMR



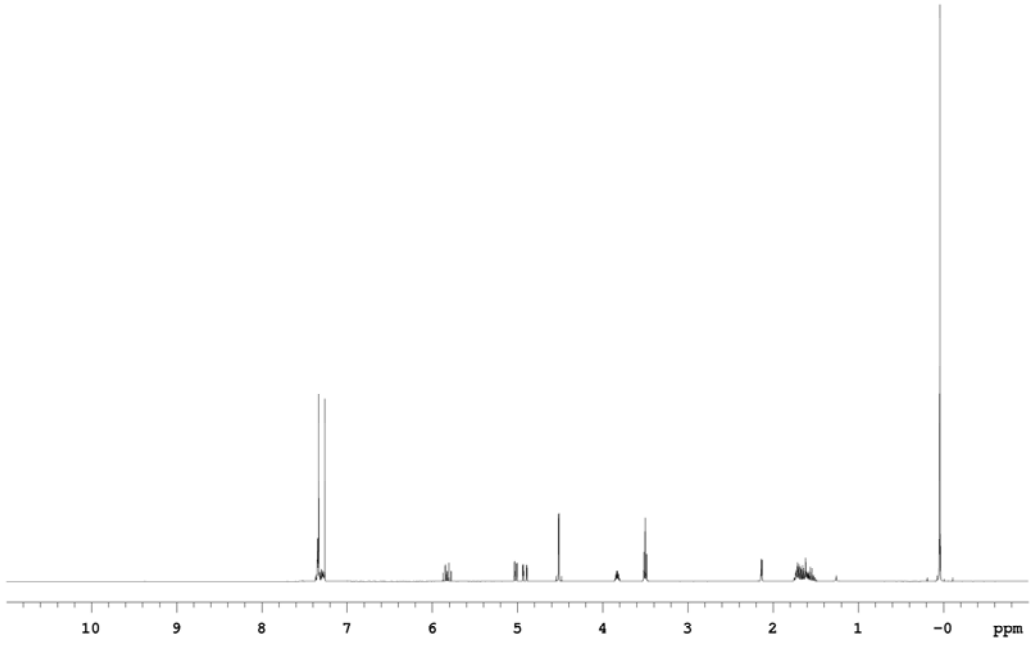
(3*R*,4*S*)-7-(benzyloxy)-3-(trimethylsilyl)hept-1-en-4-ol



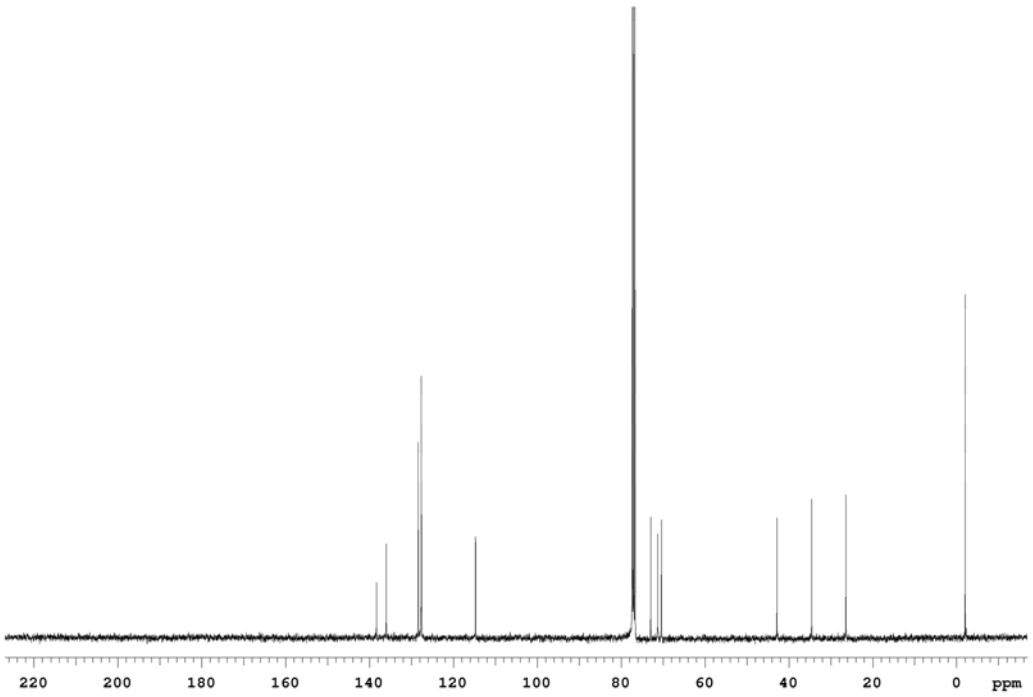
3.5h

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.83 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.02 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.91 (ddd, *J* = 16.8, 2.4, 0.8 Hz, 1H), 4.52 (m, 2H), 3.86-3.80 (m, 1H), 3.52-3.48 (m, 2H), 2.13 (d, *J* = 4.0 Hz, 1H), 1.75-1.49 (m, 5H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 136.0, 128.4, 127.6, 127.5, 114.7, 72.9, 71.2, 70.4, 42.8, 34.5, 26.4, -2.1. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 10.9 min, t_{major} = 12.2 min; ee = 95% (alcohol), 98% (aldehyde). $[\alpha]_D^{25}$= +41.2 (c =0.63, CH_2Cl_2). FTIR (neat): υ 3448, 2950, 2857, 1624, 1496, 1454, 1362, 1244, 1204, 1097, 1028, 950, 895, 835, 782, 734, 696. HRMS (CI) Calcd. for $C_{17}H_{27}O_2Si$ $[M-H]^+$: 291.1780, Found: 292.1781.

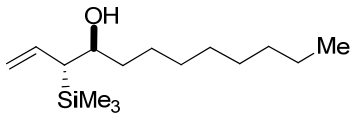
^{1}H NMR



^{13}C NMR



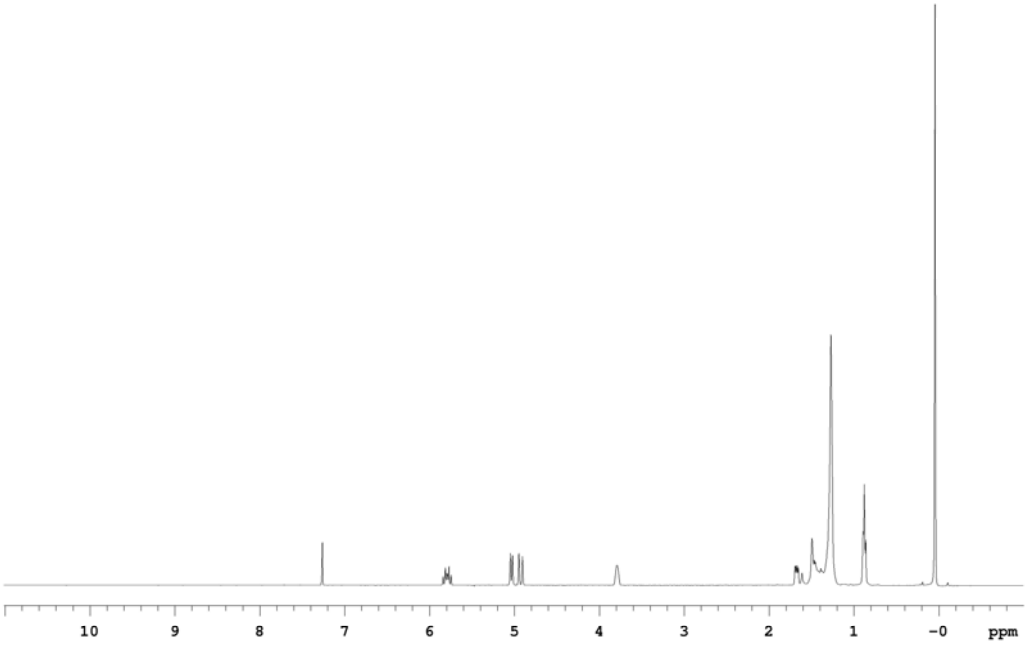
(3*R*,4*S*)-3-(trimethylsilyl)dodec-1-en-4-ol



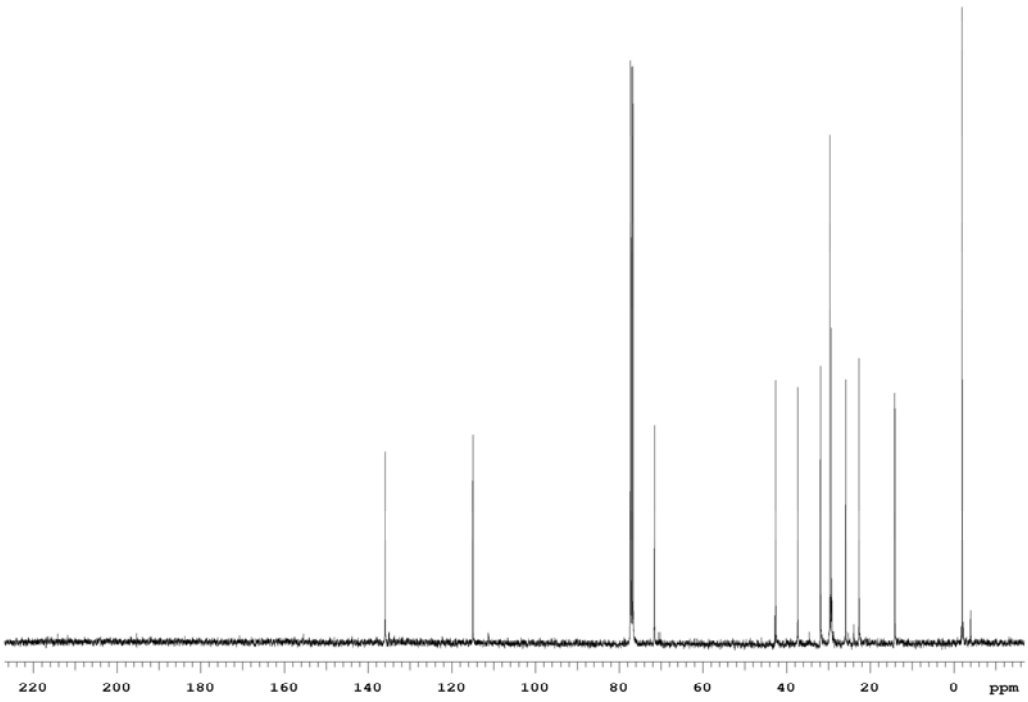
3.5i

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:10). ^1H NMR (400 MHz, $CDCl_3$): δ 5.79 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.92 (d, *J* = 17.2 Hz, 1H), 3.84-3.74 (m, 1H), 1.69-1.65 (m, 1H), 1.49-1.26 (m, 15H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 115.0, 71.5, 42.6, 37.3, 31.9, 29.6, 29.3, 25.8, 22.7, 14.1, -2.0. HPLC: Enantiomeric excess was determined by HPLC analysis of the 3,5-nitrobenzoate derivative of the product (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 10.7 min, t_{major} = 11.3 min; ee = 95% (alcohol), 90% (aldehyde). $[\alpha]_D^{25}$= +21.2 (c =0.57, CH_2Cl_2). FTIR (neat): υ 3463, 2955, 2924, 2854, 1716, 1624, 1465, 1378, 1246, 1167, 1049, 1004, 895, 836, 750, 723, 690. HRMS (CI) Calcd. for $C_{15}H_{31}OSi$ $[M-H]^+$: 255.2144, Found: 255.2132.

^{1}H NMR

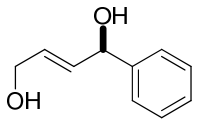


^{13}C NMR



Detailed Procedure and Spectral Data for Oxidative Elimination of Adducts 3.5a, 3.5f, 3.5g, and 3.5i.

(*R*,*E*)-1-phenylbut-2-ene-1,4-diol



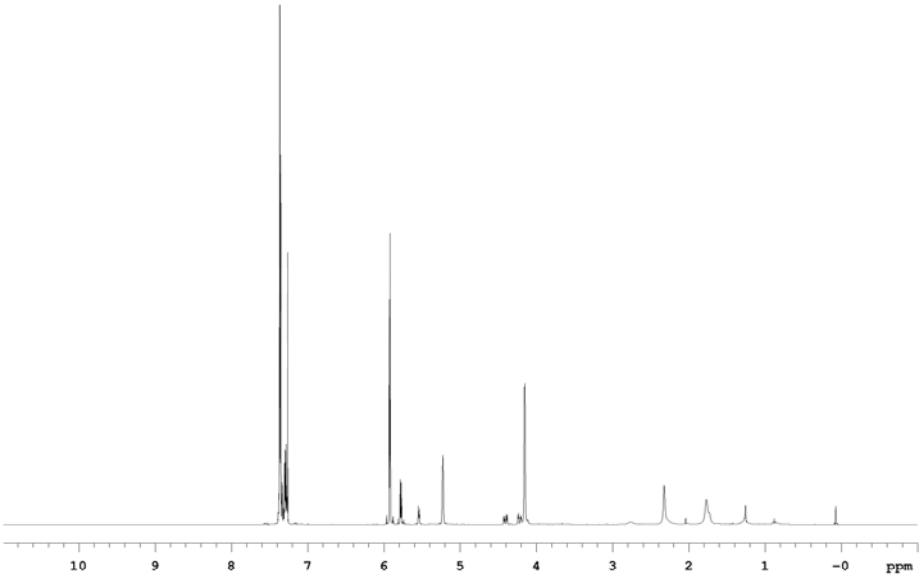
3.7a

A flask was charged with **3.5a** (33.1 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **3.7a** (19.5 mg, 0.119 mmol) as a colorless oil in 79% yield. (*E*:*Z* = 5:1)

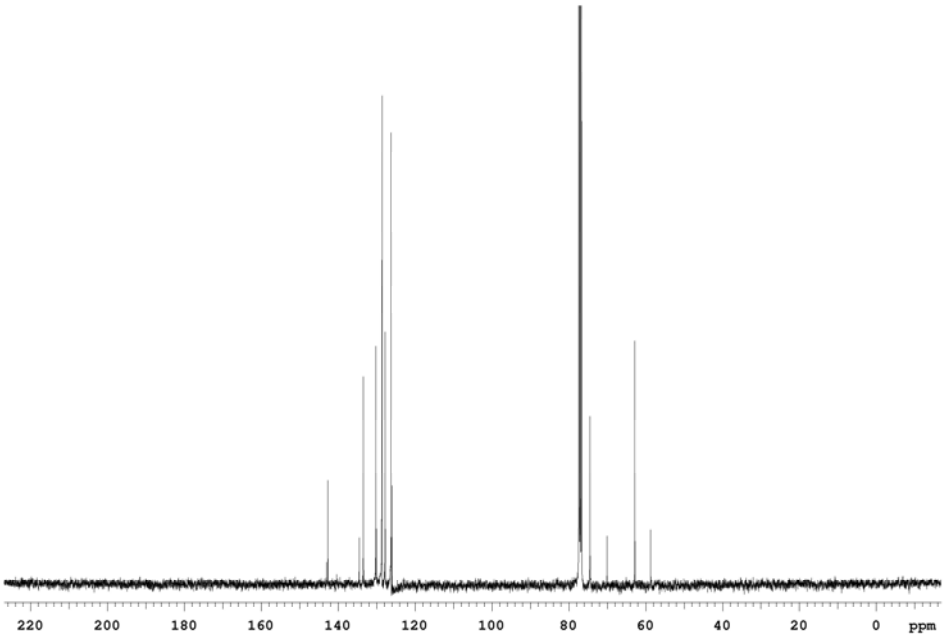
TLC (SiO_2): R_f = 0.4 (ethyl acetate:ether, 1:40). ^1H NMR for the major product (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.93-5.92 (m, 2H), 5.25-5.20 (m, 1H), 4.15 (d, *J* = 2.0 Hz, 2H), 2.32 (br, 1H), 1.77 (br, 1H). ^{13}C NMR for the major product (100 MHz, $CDCl_3$): δ 142.7, 133.4, 130.2, 128.6, 127.8, 126.2, 74.8, 63.1. FTIR (neat): υ 3304,

3029, 2859, 1492, 1452, 1261, 1193, 1086, 970, 912, 846, 751. HRMS (CI) Calcd. for $C_{10}H_{11}O_2$ $[M-H]^+$: 163.0759, Found: 163.0760.

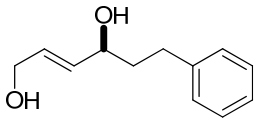
^{1}H NMR



^{13}C NMR



(*S*,*E*)-6-phenylhex-2-ene-1,4-diol

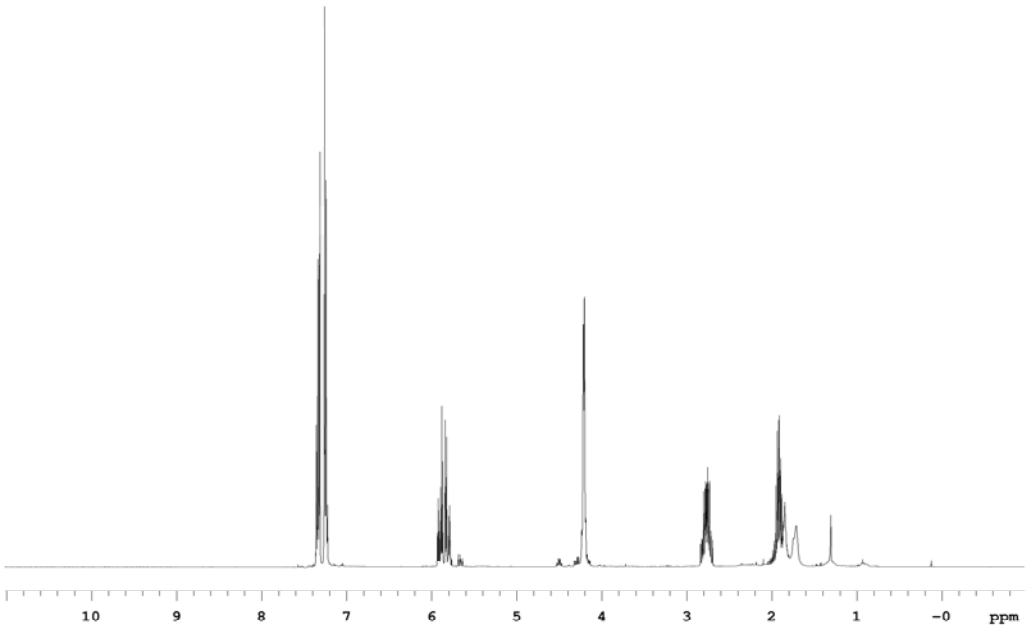


3.7f

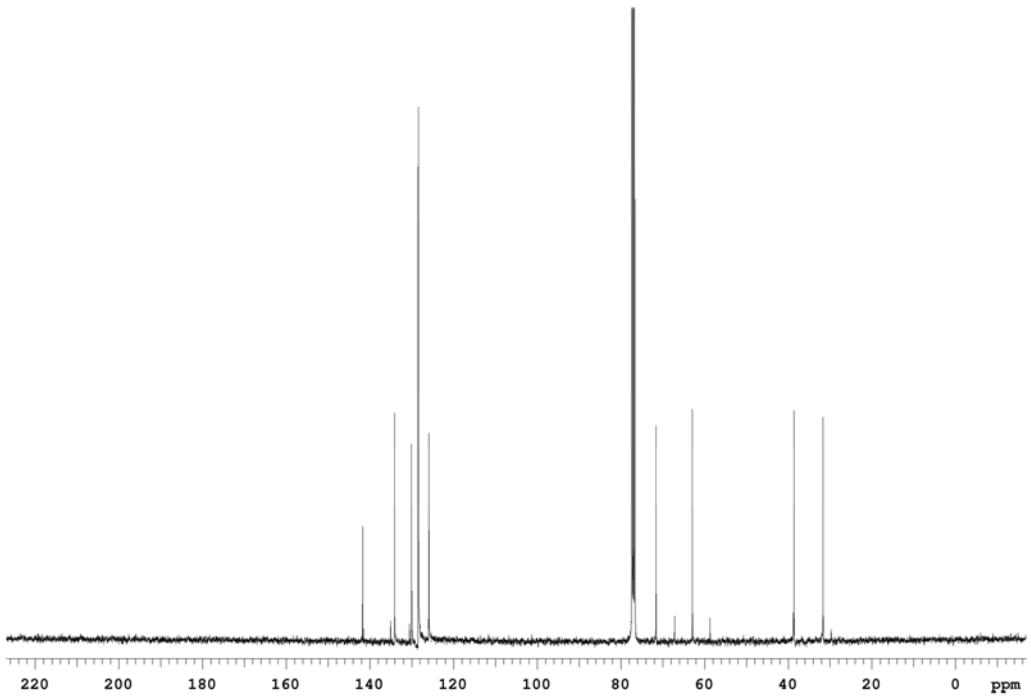
A flask was charged with **3.5f** (37.3 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **3.7f** (24.2 mg, 0.126 mmol) as a colorless oil in 84% yield. (*E*:*Z* = 10:1)

TLC (SiO_2): R_f = 0.4 (ethyl acetate:ether, 1:40). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H), 7.26-7.22 (m, 2H), 5.93-5.87 (m, 1H), 5.84-5.78 (m, 1H), 4.24-4.19 (m, 3H), 2.84-2.70 (m, 2H), 1.99-1.86 (m, 2H), 1.85 (br, 1H), 1.71 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 134.1, 130.0, 128.4, 128.4, 125.9, 71.6, 62.9, 38.6, 31.6. FTIR (neat): υ 3323, 3026, 2924, 2859, 1496, 1454, 1093, 998, 972, 912, 746, 699. HRMS (CI) Calcd. for $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, Found: 192.1151.

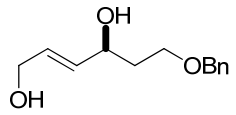
^{1}H NMR



^{13}C NMR



(*S*,*E*)-6-(benzyloxy)hex-2-ene-1,4-diol

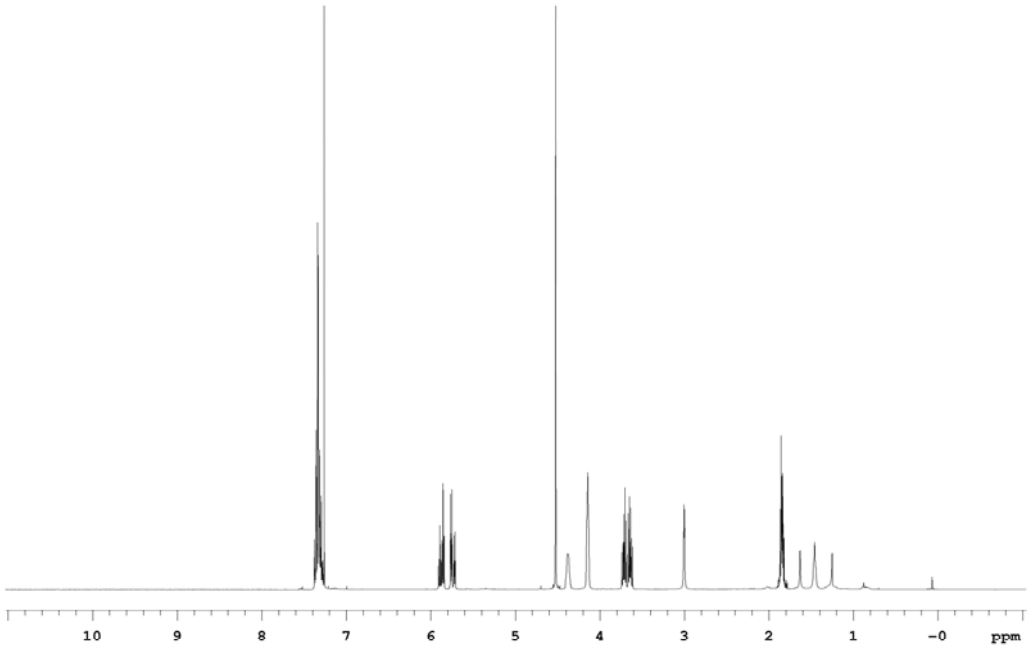


3.7g

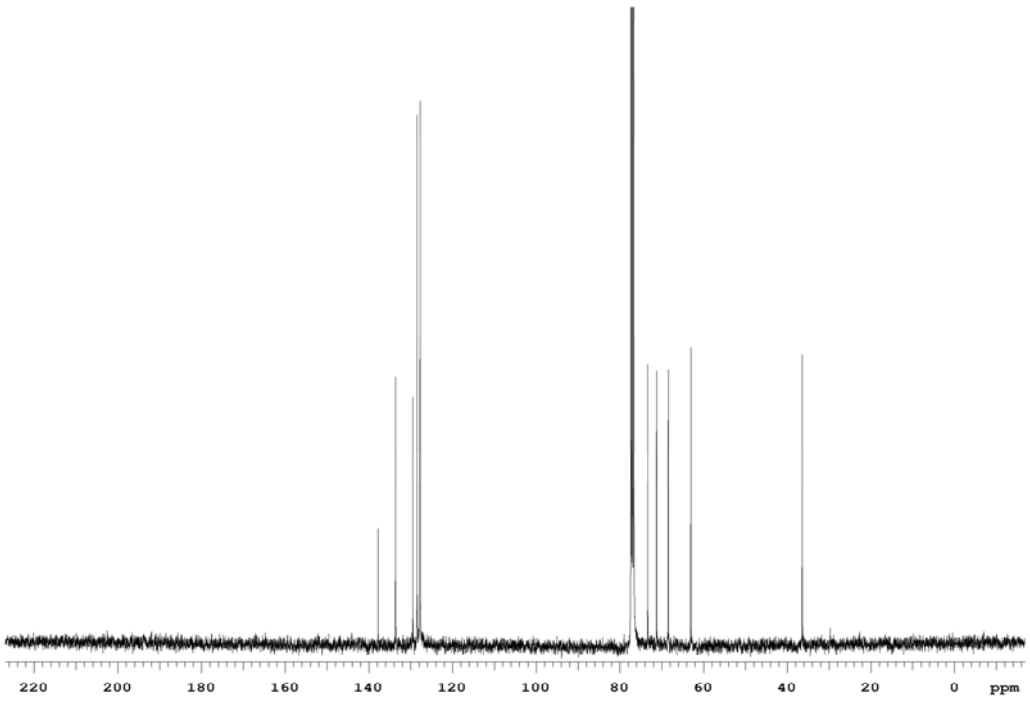
A flask was charged with **3.5g** (41.8 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **3.7g** (29.3 mg, 0.132 mmol) as a colorless oil in 88% yield. (*E*:*Z* = ≥20:1)

TLC (SiO_2): R_f = 0.4 (ethyl acetate:ether, 1:40). ^1H NMR (400 MHz, $CDCl_3$): δ 7.83-7.30 (m, 5H), 5.87 (dtd, *J* = 15.6, 5.2, 1.2 Hz, 1H), 5.74 (ddt, *J* = 15.6, 6.0, 1.2 Hz, 1H), 4.52 (s, 2H), 4.41-4.34 (m, 1H), 4.17-4.12 (m, 2H), 3.74-3.61 (m, 2H), 3.00 (d, *J* = 3.6 Hz, 1H), 1.88-1.79 (m, 2H), 1.46 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 133.6, 129.5, 128.5, 127.8, 127.7, 73.3, 71.2, 68.4, 63.0, 36.4. FTIR (neat): υ 3346, 2921, 2860, 1496, 1454, 1414, 1364, 1310, 1206, 1072, 1004, 969, 909, 802, 736. HRMS (CI) Calcd. for $C_{13}H_{17}O_3$ $[M-H]^+$: 221.1178, Found: 222.1181.

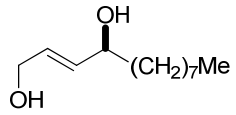
^{1}H NMR



^{13}C NMR



(*S*,*E*)-dodec-2-ene-1,4-diol

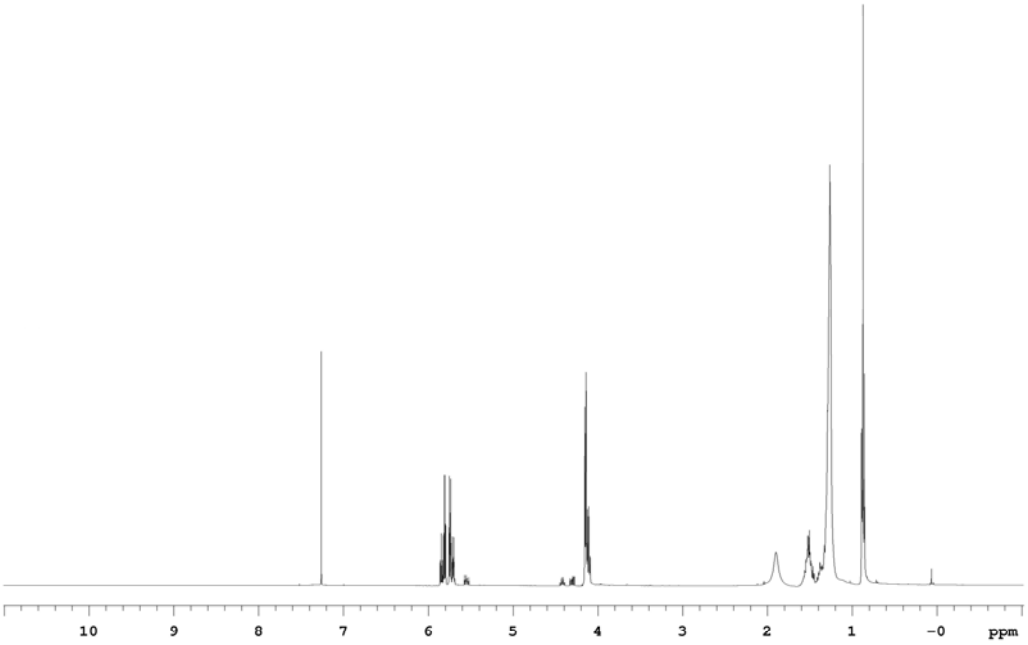


3.7i

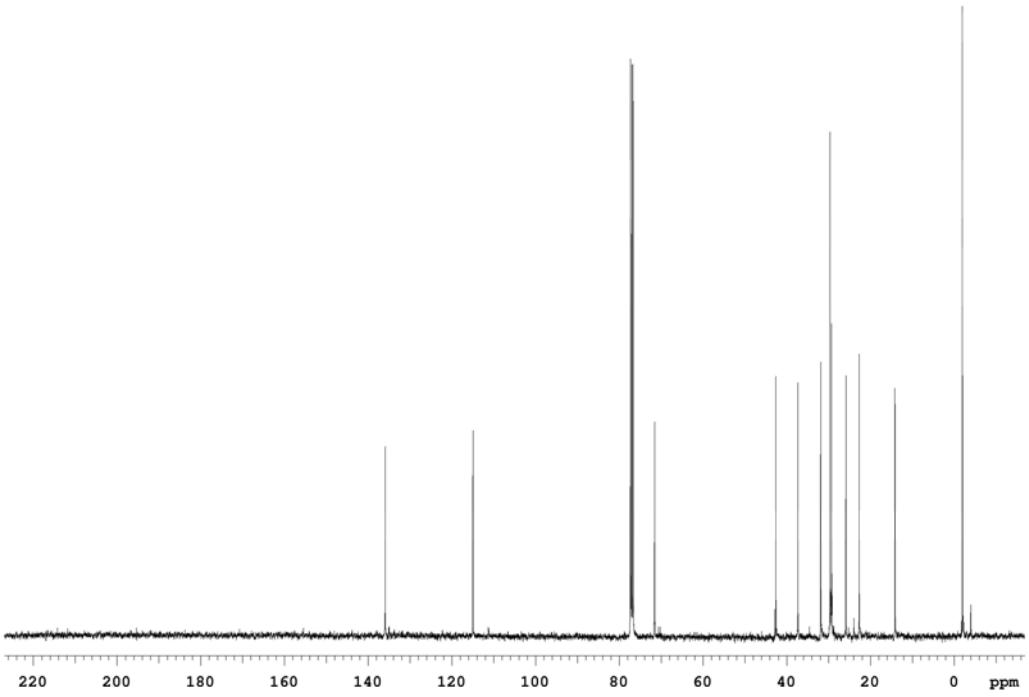
A flask was charged with **3.5i** (38.5 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **3.7i** (26.1 mg, 0.131 mmol) as a colorless oil in 87% yield. (*E*:*Z* = 10:1)

TLC (SiO_2): R_f = 0.5 (ethyl acetate:ether, 1:40). ^1H NMR (400 MHz, $CDCl_3$): δ 5.89-5.79 (m, 1H), 5.76-5.69 (m, 1H), 4.15-4.09 (m, 3H), 1.90 (br, 2H), 1.57-1.45 (m, 2H), 1.33-1.20 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 129.7, 72.3, 62.9, 37.2, 31.8, 29.5, 29.2, 25.4, 25.3, 22.6, 14.1. FTIR (neat): υ 3332, 2854, 1465, 1085, 1005, 971, 722. HRMS (CI) Calcd. for $C_{12}H_{23}O_2$ $[M-H]^+$: 199.1698, Found: 199.1699.

^{1}H NMR

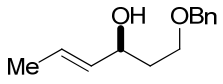


^{13}C NMR



Detailed Procedure and Spectral Data for Proto-desilylation of Adduct 3.5g.

(*S*,*E*)-1-(benzyloxy)hex-4-en-3-ol



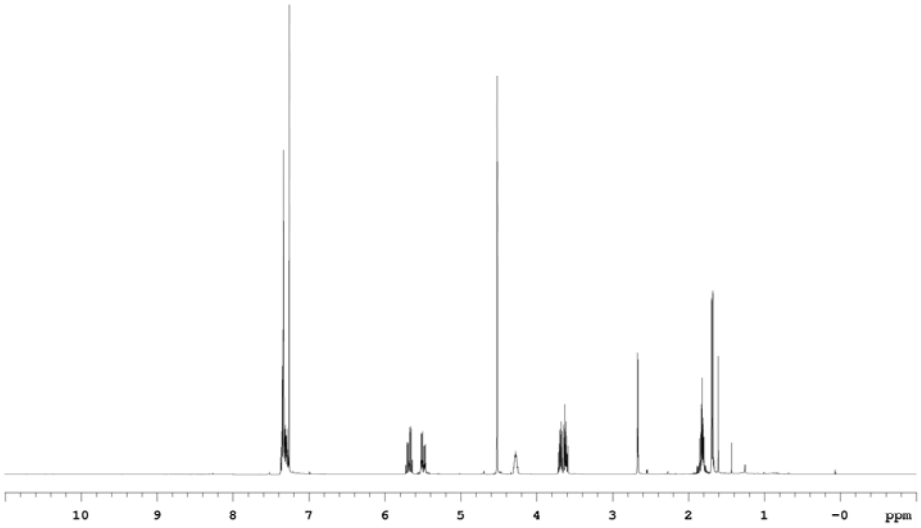
3.8g

A flask was charged with **3.5g** (30.2 mg, 0.11 mmol, 100 mol%), 4-nitrobenzaldehyde (18.1 mg, 0.12 mmol, 110 mol%) and DCM (1.2 mL, 0.9 M). The mixture was cooled to -78 ^{o}C, and then 1.0 M solution of $TiCl_4$ in DCM (0.14 mL, 0.14 mmol, 130 mol%) was added dropwise over 3 min. The resulting mixture was stirred until no starting material left (checked by TLC). The mixture was quenched with sat'd aqueous ammonium chloride solution (3 mL) at -78 ^{o}C, and then diluted with DCM (3 mL). The resulting biphasic solution was warmed to ambient temperature and stirred for 10 min. The organic phase was separated and the aqueous was washed with DCM. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether:hexanes, 1:4) provided **3.8g** (16.6 mg, 0.08 mmol) as a colorless oil in 73% yield.

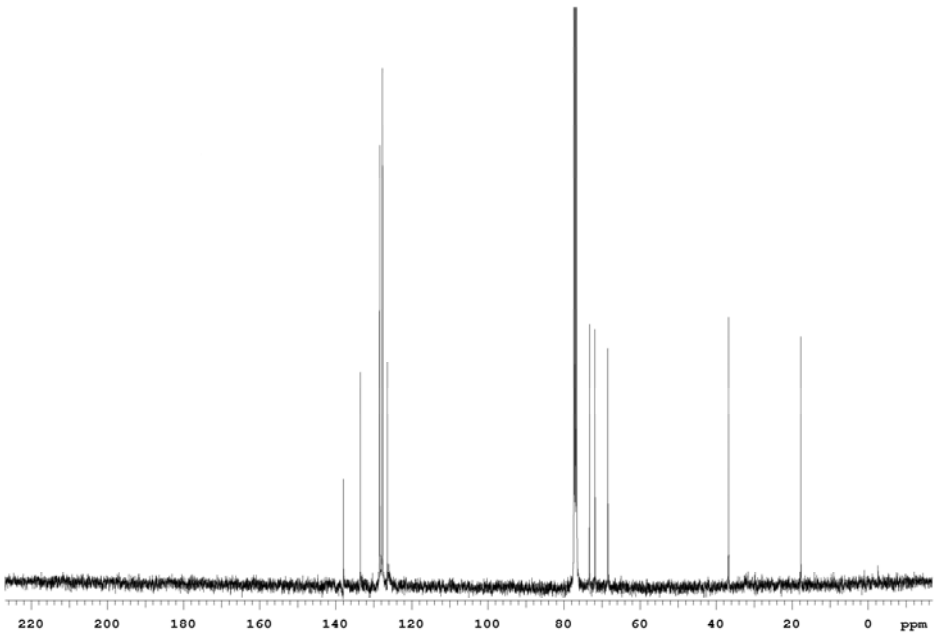
TLC (SiO_2): R_f = 0.15 (ethyl acetate:hexanes, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.37 (m, 5H), 5.67 (dqd, *J* = 15.2, 6.4, 0.8 Hz, 1H), 5.49 (dqd, *J* = 15.2, 6.4, 1.6 Hz, 1H), 4.52 (s, 2H), 4.25-4.31 (m, 1H), 3.72-3.66 (m, 1H), 3.65-3.59 (m, 1H), 2.67 (d, *J* = 3.2 Hz, 1H), 1.85-1.75 (m, 2H), 1.69 (ddd, *J* = 6.8, 1.6, 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 133.5, 128.4, 127.7, 127.6, 126.4, 73.2, 71.8, 68.4, 36.7, 17.7. FTIR

(neat): υ 3414, 3029, 2916, 2857, 1496, 1453, 1364, 1309, 1205, 1096, 966, 923, 801, 736. HRMS (CI) Calcd. for $C_{13}H_{17}O_2$ $[M-H]^+$: 205.1229, Found: 205.1227.

^{1}H NMR

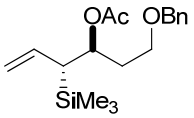


^{13}C NMR



Detailed Procedure and Spectral Data for [3+2] Cycloaddition of Adduct 3.5g.

(3*S*,4*R*)-1-(benzyloxy)-4-(trimethylsilyl)hex-5-en-3-yl acetate

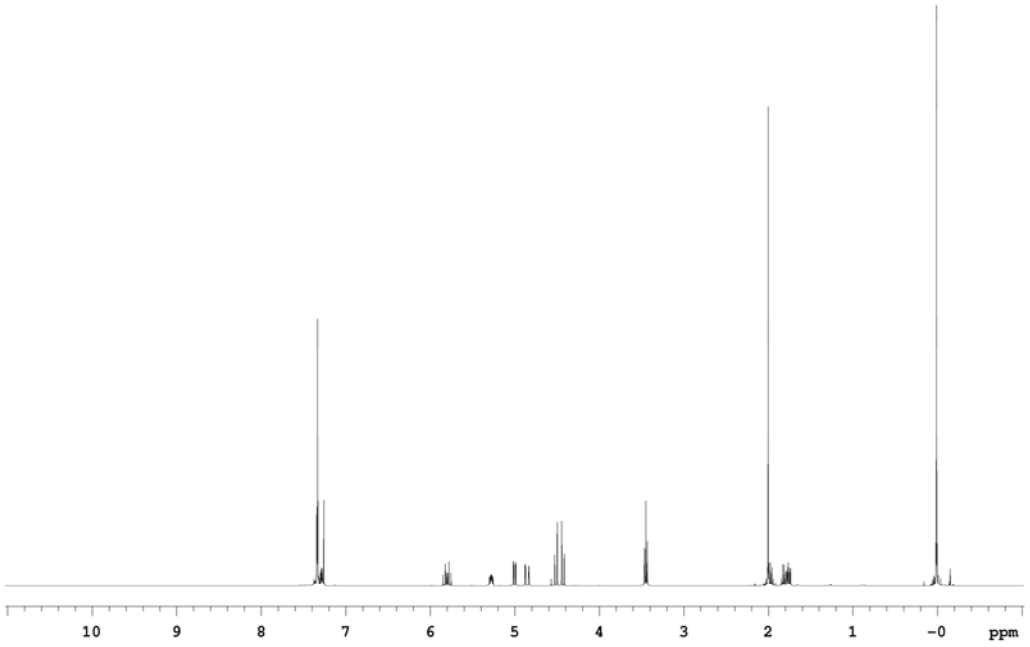


3.5g-OAc

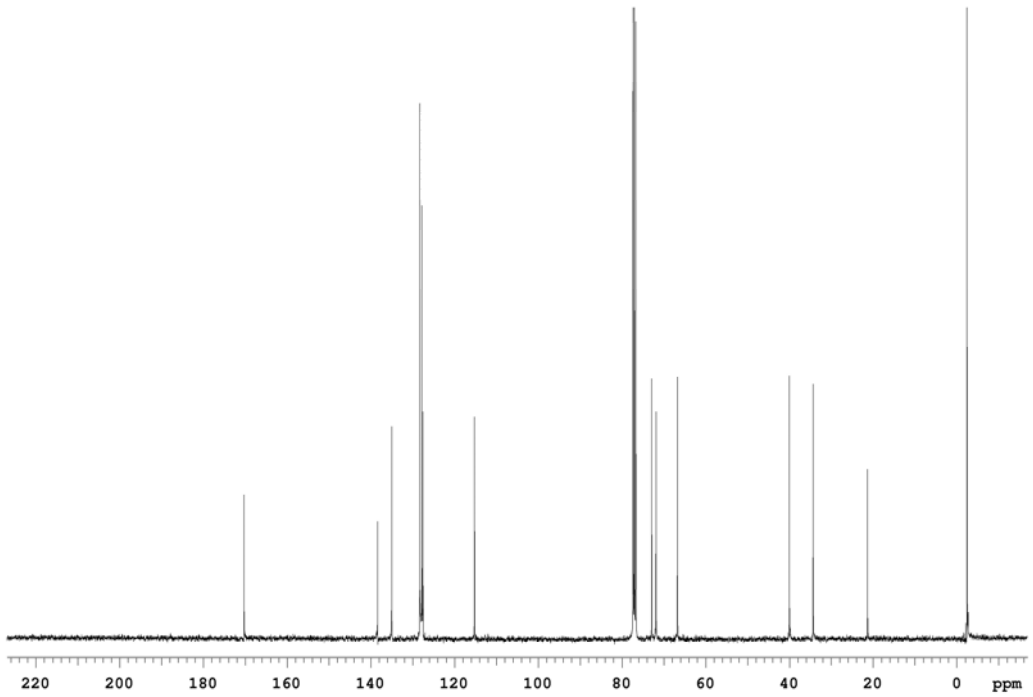
To a cooled (0 ^{o}C) suspension of **3.5g** (100 mg, 0.36 mmol, 100 mol%), DMAP (4.4 mg, 0.036 mmol, 10 mol%) and Et_3N (72.9 mg, 0.72 mmol, 200 mol%) in DCM (4.0 mL, 0.09 M) was added acetic anhydride (73.8 mg, 0.72 mmol, 200 mol%). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The mixture was washed with sat'd aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:30 with 0.1% TEA) provided **3.5g-OAc** (114.2 mg, 0.36 mmol) as a colorless oil in 99% yield.

TLC (SiO_2): R_f = 0.70 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 5.80 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.28 (dq, *J* = 6.0, 3.6 Hz, 1H), 5.00 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.85 (ddd, *J* = 17.2, 2.0, 0.4 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.05-1.92 (m, 1H), 2.00 (s, 3H), 1.84-1.74 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 138.4, 135.0, 128.3, 127.8, 127.5, 115.2, 72.9, 71.9, 66.7, 40.0, 34.3, 21.3, -2.4. FTIR (neat): υ 3031, 2954, 2860, 1737, 1626, 1496, 1454, 1370, 1236, 1102, 1019, 953, 902, 838, 748, 697.

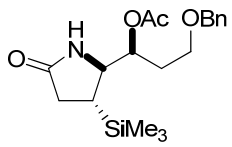
^{1}H NMR



^{13}C NMR



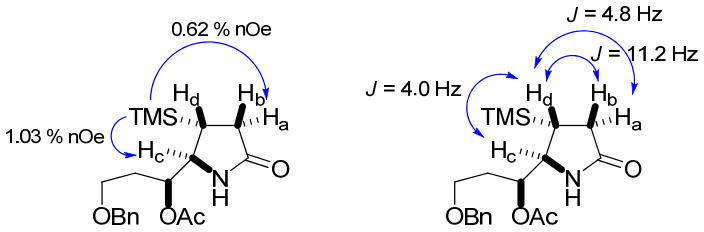
(1*S*)-3-(benzyloxy)-1-((3*R*)-5-oxo-3-(trimethylsilyl)pyrrolidin-2-yl)propyl acetate



3.9g

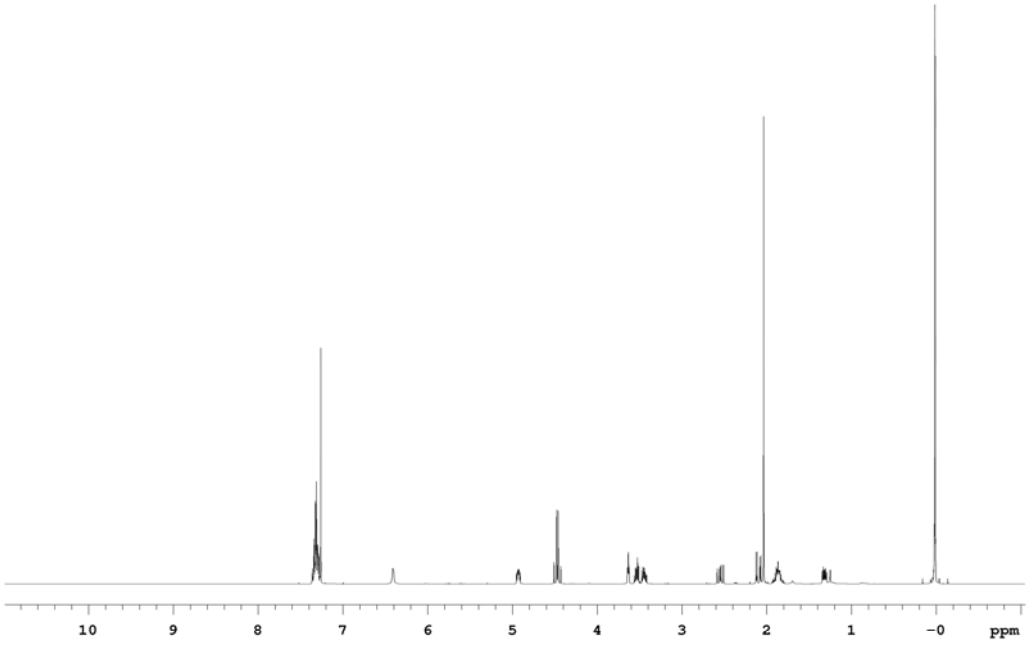
To a cooled (0 ^{o}C) suspension of **3.5g-OAc** (15 mg, 0.047 mmol, 100 mol%) and $NaHCO_3$ (10 mg, 0.12 mmol, 250 mol%) in toluene (0.5 mL, 0.1 M) was added chlorosulfonyl isocynate (10.9 mg, 0.071 mmol, 150 mol%). The reaction mixture was warmed slowly to ambient temperature and stirred for 10 hr. Sat'd aqueous $NaHSO_3$ (0.5 mL) was added and stirred 16 hr, at which point the layers were separated and the aqueous was extracted with EtOAc. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:2.5) provided **3.9g** (13.3 mg, 0.037 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.2 (ethyl acetate:hexanes, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 6.41 (br, 1H), 4.95-4.91 (m, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.63 (t, *J* = 4.0 Hz, 1H), 3.56-3.42 (m, 2H), 2.55 (dd, *J* = 17.6, 11.2 Hz, 1H), 2.10 (dd, *J* = 17.6, 4.8, 1H), 2.04 (s, 3H), 1.94-1.81 (m, 2H), 1.32 (ddd, *J* = 11.2, 4.8, 4.0 Hz, 1H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 170.6, 137.8, 128.4, 127.9, 127.8, 73.8, 73.4, 66.1, 57.7, 31.4, 31.3, 22.0, 21.1, -3.8. FTIR (neat): υ 3211, 2953, 1737, 1691, 1496, 1454, 1370, 1232, 1096, 1027, 964, 837, 738, 698. HRMS (CI) Calcd. for $C_{19}H_{30}NO_4Si$ $[M+H]^+$: 364.1944, Found: 364.1946.

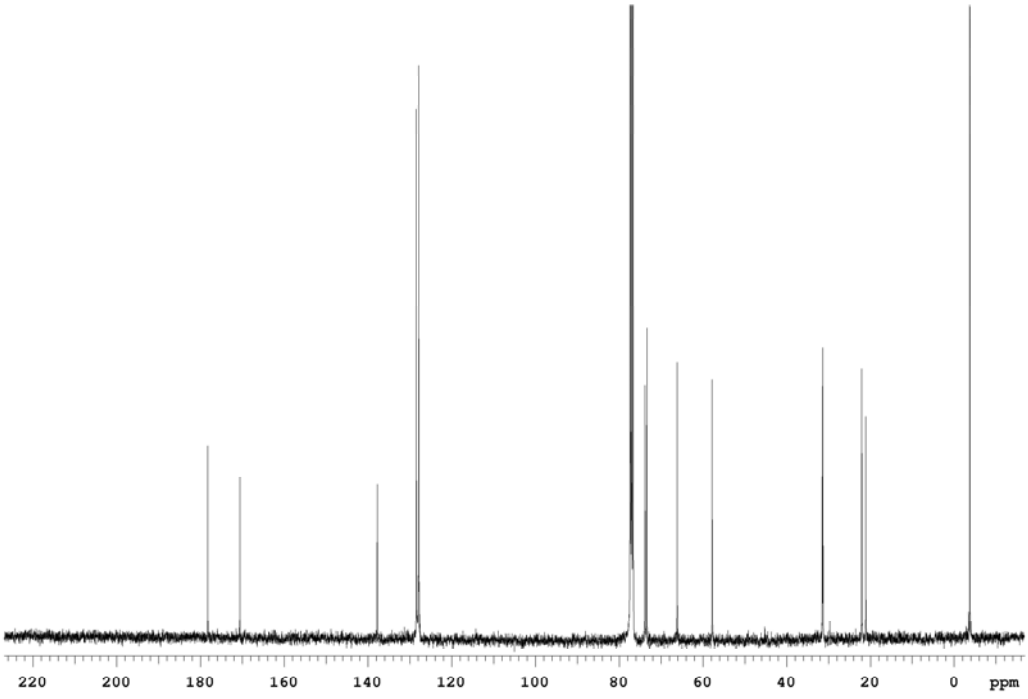


NOE experiment was performed for **3.9g** using a pure sample. TMS irradiated: H_a (0.62%), H_C (1.03%). (Note: The observation of nOe between TMS and H_c and the absence of nOe between TMS and the OAc suggest a 1,2 trans configuration which is corresponding to the coupling constant calculation and the stereochemistry model proposed by Woerpel.)

^{1}H NMR



^{13}C NMR



Preparation of *BIPHEP*-I

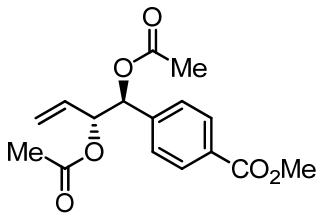
To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), BIPHEP (136 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^{o}C, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in*

vacuo and hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (108 mg, 0.11 mmol, 88% yield).

Preparation of (*R*)-*SEGPHOS*-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*R*)-SEGPHOS (159 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (101 mg, 0.098 mmol, 75% yield).

1-(4-(methoxycarbonyl)phenyl)but-3-ene-1,2-diyl diacetate



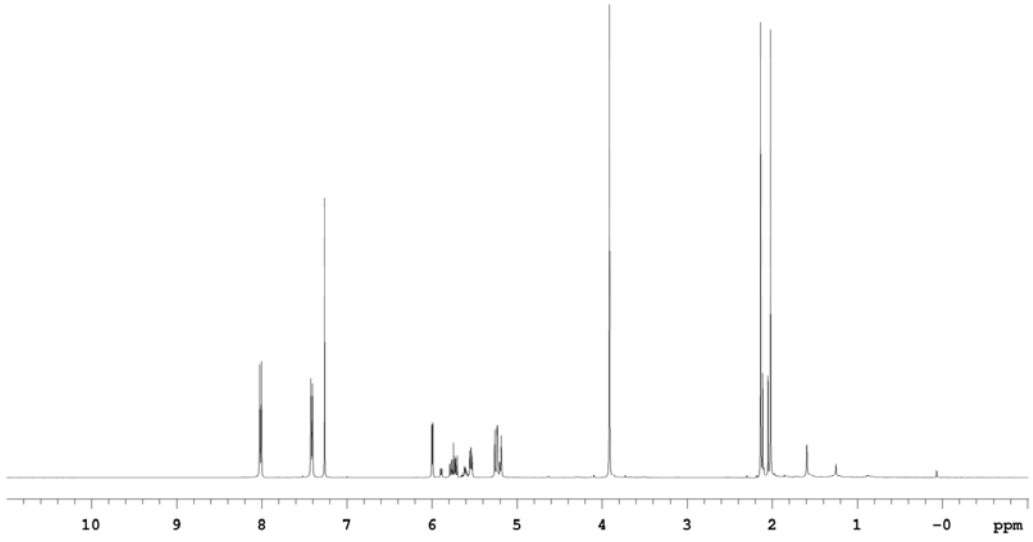
3.12c (a)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with *BIPHEP*-I (9.5 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Methyl 4-

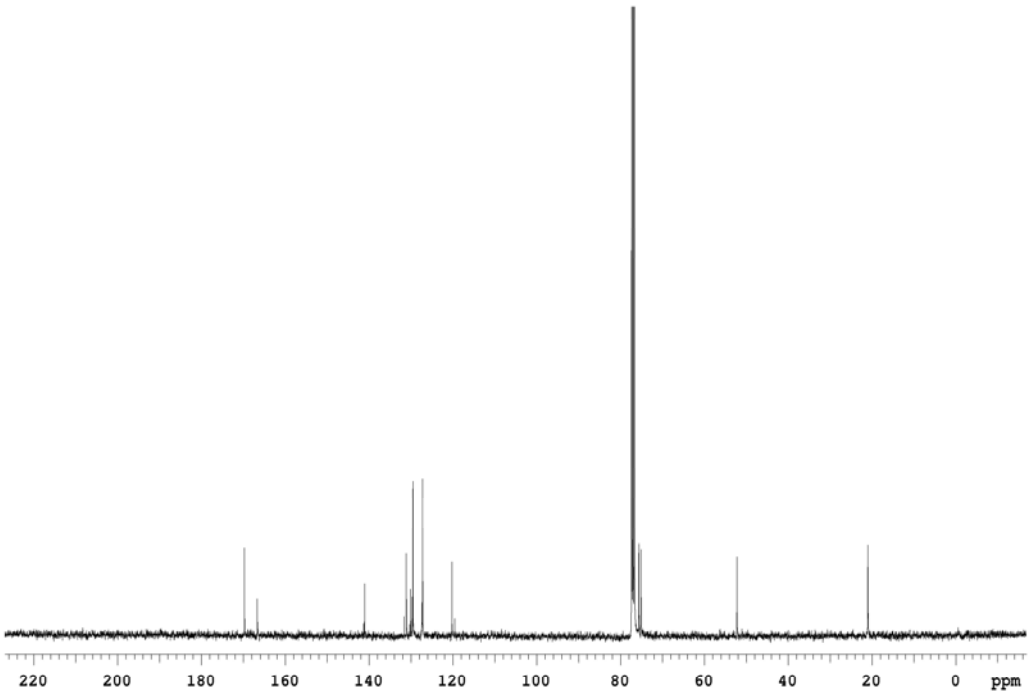
formylbenzoate **3.11c** (32.8 mg, 0.2 mmol, 100 mol%), acrolein *gem*-diacetate **3.10a** (63 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. Acetyl chloride (71 μL, 1.0 mmol, 500 mol%), Et_3N (270 μL , 2.0 mmol, 1000 mol%), DMAP (1.2 mg , 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.6 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 20 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:7) provided **3.12c (a)** (45 mg, 0.148 mmol) as a colorless oil in 74% yield (4:1 dr).

^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 5.99 (d, J = 4.8 Hz, 1H), 5.79-5.70 (m, 1H), 5.55-5.53 (m, 1H), 5.26-5.18 (m, 2H), 3.91 (s, 3H), 2.14 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ169.7, 166.7, 141.1, 131.1, 130.1, 129.7, 129.5, 127.2, 120.2, 75.6, 75.0, 52.2, 21.0, 20.9. FTIR (neat): 1721, 1437, 1372, 1281, 1222, 1111, 1020, 988, 906, 816, 727 cm^{-1}.

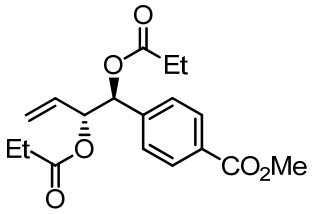
^{1}H NMR



^{13}C NMR



1-(4-(methoxycarbonyl)phenyl)but-3-ene-1,2-diyl dipropionate



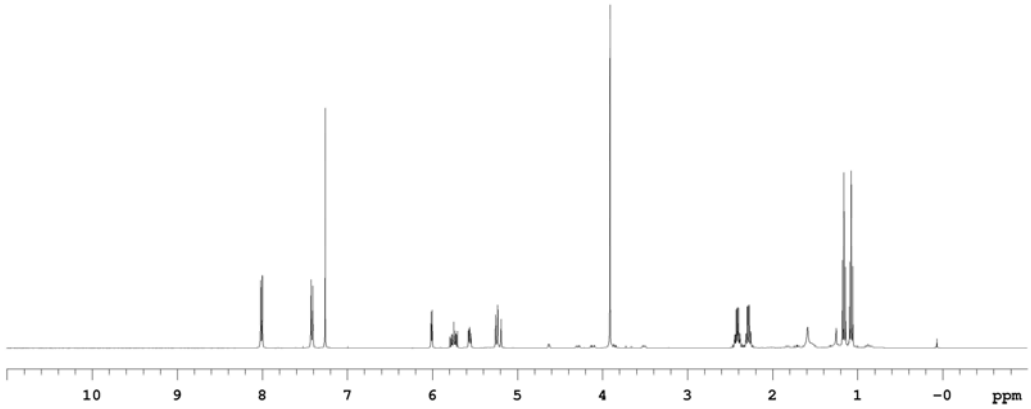
3.12c (b)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with *BIPHEP*-I (9.5 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Methyl 4-formylbenzoate **3.11c** (32.8 mg, 0.2 mmol, 100 mol%), acrolein *gem*-dipropionate **3.10b** (74 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. Propionyl chloride (87 μL, 1.0 mmol, 500 mol%), Et_3N (270 μL, 2.0 mmol, 1000 mol%), DMAP (1.2 mg , 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.6 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 20 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:9) provided **3.12c (b)** (43 mg, 0.13 mmol) as a colorless oil in 65% yield (5:1 dr).

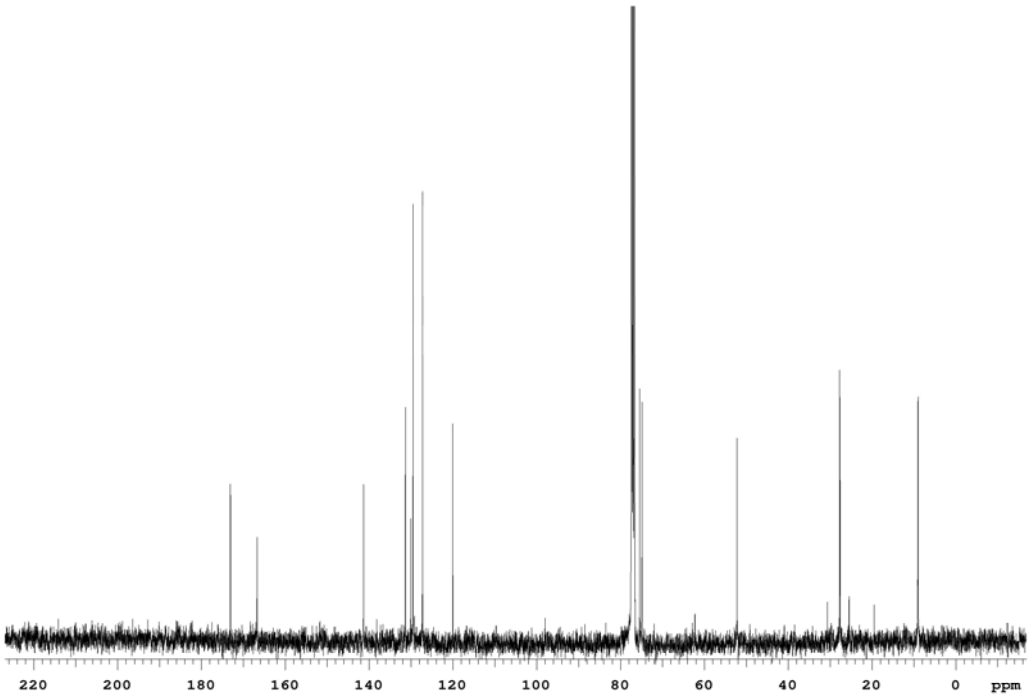
^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 6.01 (d, J = 5.2 Hz, 1H), 5.79-5.71 (m, 1H), 5.58-5.55 (m, 1H), 5.26-5.19 (m, 2H), 3.91 (s, 3H),

2.41 (qd, J = 7.6, 2.8 Hz, 2H), 2.28 (qd, J = 7.6, 2.0 Hz, 2H), 1.16 (t, J = 7.6 Hz, 3H), 1.08 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ173.1 (two carbons are overlapped), 166.7, 141.3, 131.2, 130.0, 129.5, 127.2, 120.0, 75.4, 74.8, 52.2, 27.7, 27.6, 9.0, 8.9. FTIR (neat): 1724, 1437, 1281, 1181, 1113, 1083, 1019, 905, 726 cm^{-1}.

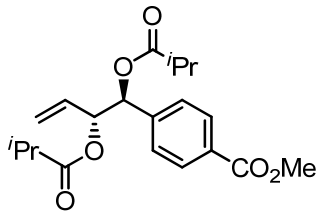
^{1}H NMR



^{13}C NMR



1-(4-(methoxycarbonyl)phenyl)but-3-ene-1,2-diyl bis(2-methylpropanoate)



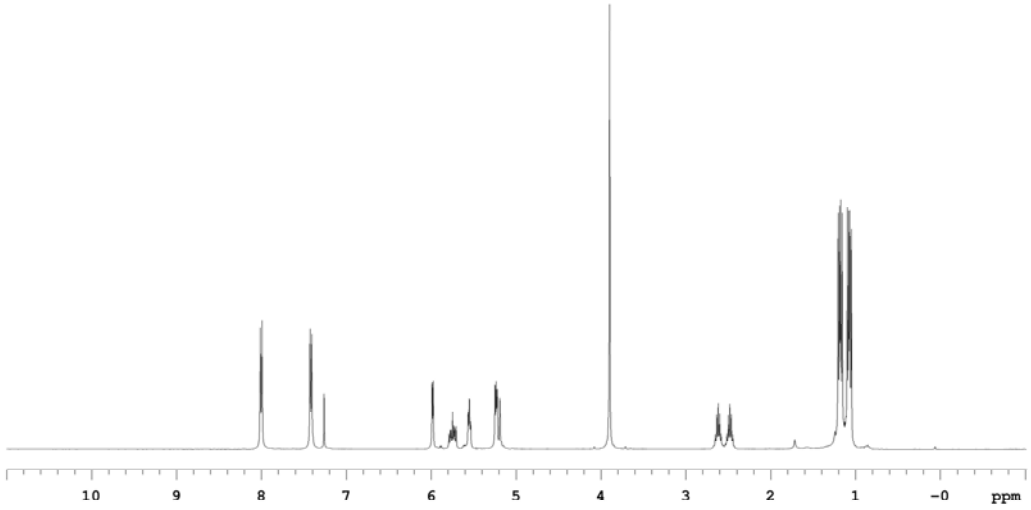
3.12c (c)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with *BIPHEP*-I (9.5 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Methyl 4-formylbenzoate **3.11c** (32.8 mg, 0.2 mmol, 100 mol%), acrolein *gem*-diisobutyrate **3.10c** (86 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. Isobutyryl chloride (105 μL, 1.0 mmol, 500 mol%), Et_3N (270 μL , 2.0 mmol, 1000 mol%), DMAP (1.2 mg , 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.6 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 20 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:15) provided **3.12c (c)** (23 mg, 0.064 mmol) as a colorless oil in 32% yield (8:1 dr).

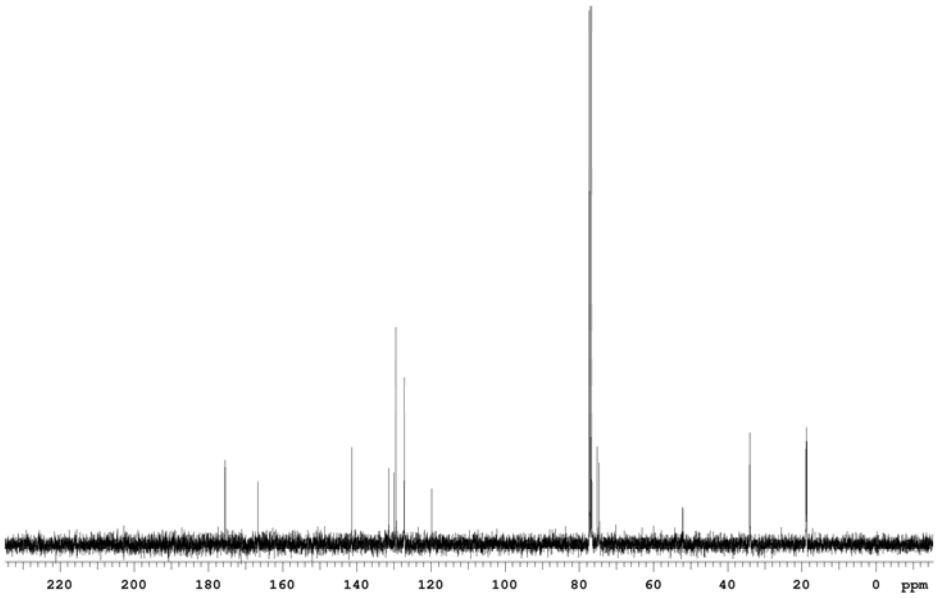
^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 5.98 (d, J = 5.2 Hz, 1H), 5.79-5.70 (m, 1H), 5.56-5.53 (m, 1H), 5.25-5.19 (m, 2H), 3.90 (s, 3H),

2.65-2.45 (m, 2H), 1.20-1.16 (m, 6H), 1.10-1.15 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 175.4, 166.6, 141.4, 131.4, 130.0, 129.4, 127.2, 119.8, 75.2, 74.6, 52.1, 34.0 (two carbons are overlapped), 18.9, 18.8. FTIR (neat): 1725, 1470, 1437, 1388, 1281, 1189, 1149, 1112, 1069, 1020, 989, 906, 854, 727 cm^{-1}.

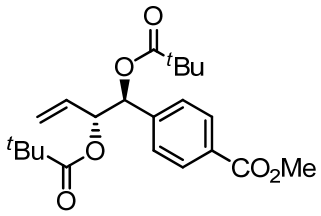
^{1}H NMR



^{13}C NMR



1-(4-(methoxycarbonyl)phenyl)but-3-ene-1,2-diyl bis(2,2-dimethylpropanoate)



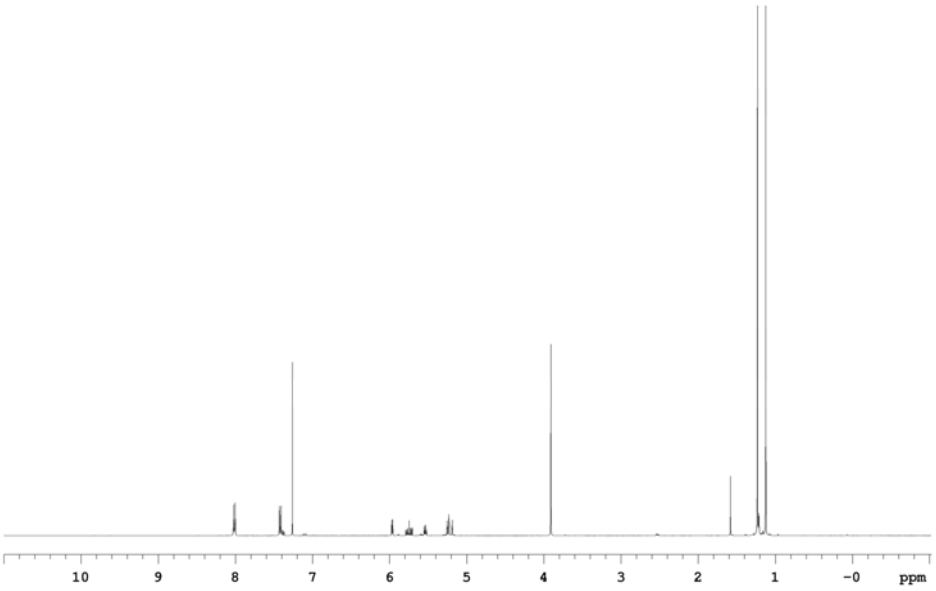
3.12c (d)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with *BIPHEP*-I (9.5 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Methyl 4-formylbenzoate **3.11c** (32.8 mg, 0.2 mmol, 100 mol%), acrolein *gem*-dipivalate **3.10d** (97 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. Pivaloyl chloride (123 μL, 1.0 mmol, 500 mol%), Et_3N (270 μL , 2.0 mmol, 1000 mol%), DMAP (1.2 mg , 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.6 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 20 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:20) provided **3.12c (d)** (12 mg, 0.003 mmol) as a colorless oil in 15% yield (10:1 dr).

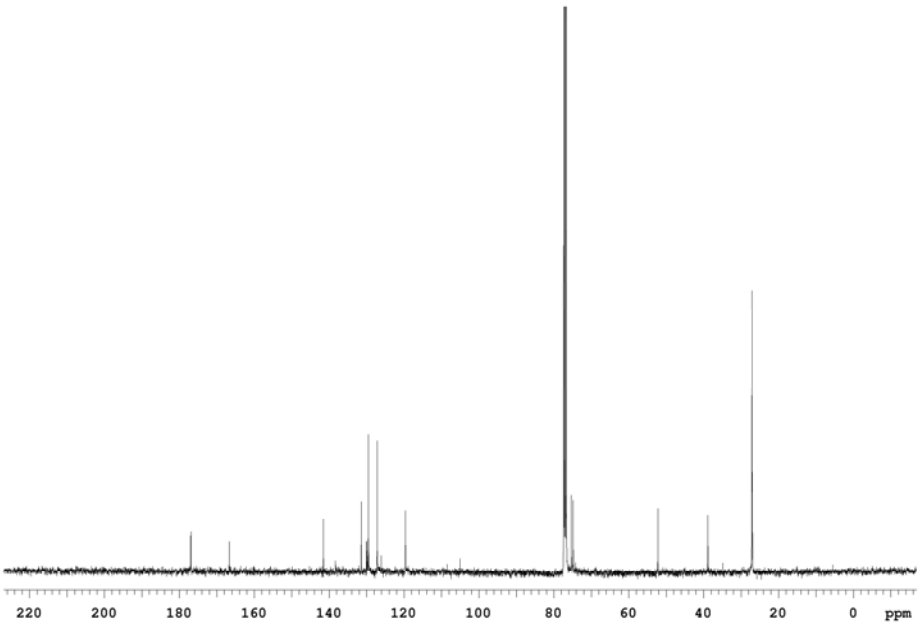
^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 5.97 (d, J = 5.2 Hz, 1H), 5.79-5.71 (m, 1H), 5.55-5.52 (m, 1H), 5.26-5.19 (m, 2H), 3.91(s, 3H),

1.23 (s, 9H), 1.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 176.8, 166.7, 141.5, 131.4, 129.8, 129.5, 127.2, 119.6, 75.3, 74.8, 52.2, 38.9, 38.8, 27.1, 27.0. FTIR (neat): 1725, 1479, 1437, 1397, 1279, 1140, 1020, 988, 907, 729 cm^{-1}.

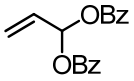
^{1}H NMR



^{13}C NMR



Acrolein *gem*-dibenzoate

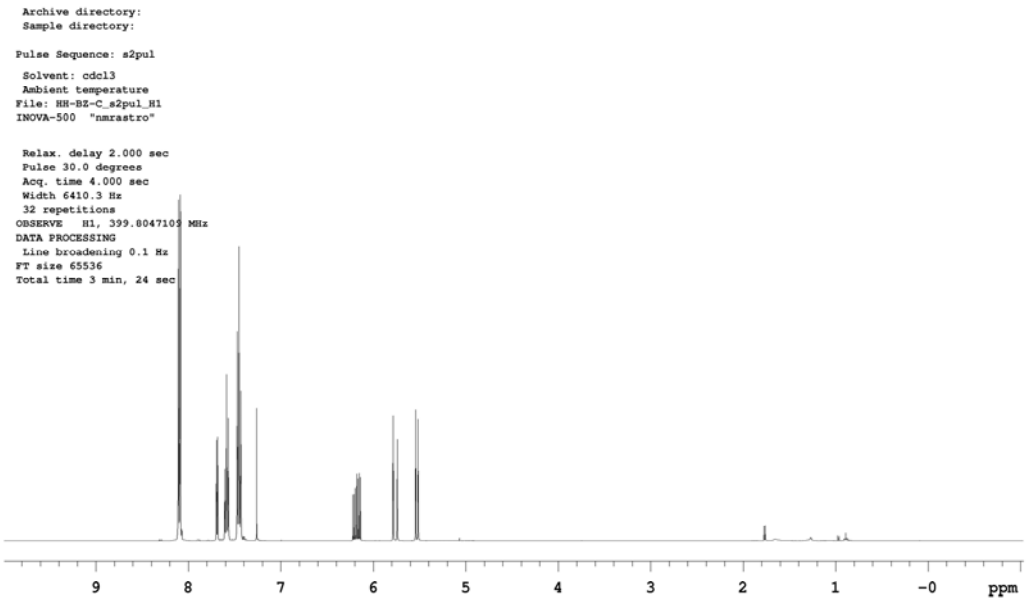


3.10e

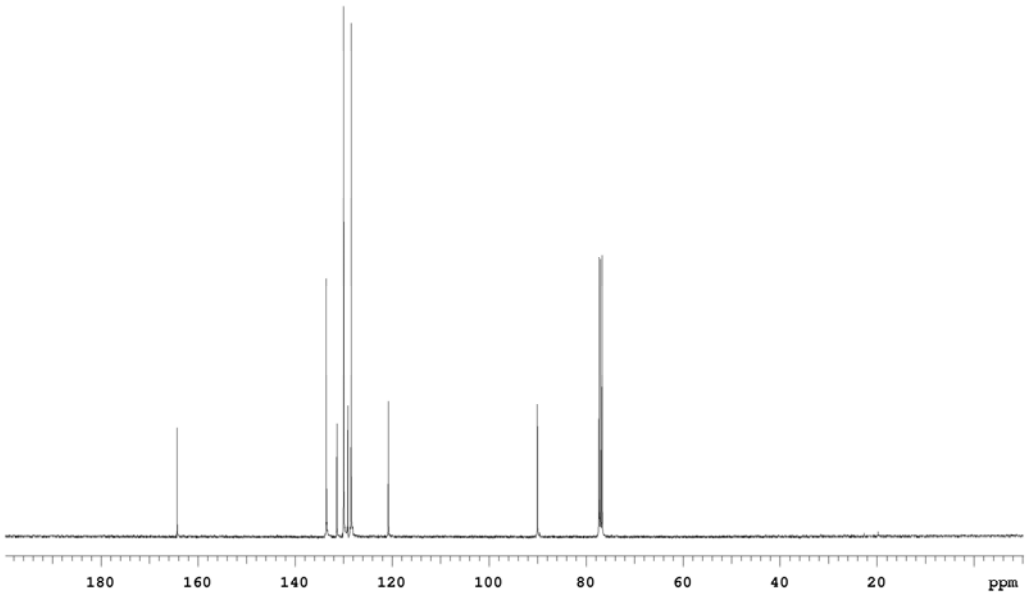
3 drops of H_2SO_4 were added to a solution of benzoic anhydride (22.6 g, 100 mmol, 100 mol%) in CH_2Cl_2 (1.0 M, 100 mL). A solution of freshly distilled acrolein (10 mL, 150 mmol, 150 mol%) in CH_2Cl_2 (10 mL) was added drop by drop, at a rate slow enough to maintain the solution at ambient temperature. The reaction mixture was stirred at ambient temperature for 72 hr and filtered through a short pad of K_2CO_3. The solvent was removed *in vacuo* and the residue was disolved in hexane. Filtration, evaporation *in vacuo* and purification of the residue by column chromatography (SiO_2; hexanes: TEA, 150:1) provided **3.10e** (14 g, 50 mmol) as a colorless oil in 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.07 (m, 4H), 7.70-7.68 (m, 1H), 7.61-7.56 (m, 2H), 7.48-7.43 (m, 4H), 6.18 (dq, *J* = 17.2, 5.2 Hz, 1H), 5.76 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.43 (dt, *J* = 10.8, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 133.5, 131.4, 130.0, 129.1, 128.4, 120.7, 90.0. FTIR (neat): 1736, 1601, 1452, 1316, 1274, 1243, 1178, 1115, 1079, 1059, 1023, 949, 906, 801, 729, 707, 686 cm^{-1}.HRMS (CI) Calcd. for $C_{17}H_{14}O_4$ $[M]^+$: 282.0892, Found: 282.0888.

^{1}H NMR



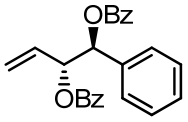
^{13}C NMR



General procedure for *anti*-Diastereo- and Enantioselective Carbonyl Alkoxyallylation

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with *(R)-SEGPHOS*-**I** (10.3 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Aldehyde (0.2 mmol, 100 mol%), acrolein *gem*-dibenzoate **3.10e** (113 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 72 hr, at which point the reaction mixture was cooled to ambient temperature. Benzoyl chloride (116 μL, 1.0 mmol, 500 mol%), Et_3N (270 μL , 2.0 mmol, 1000 mol%), DMAP (1.2 mg , 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.6 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 20 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:10) provided the corresponding product.

(1*S*, 2*R*)-1-phenylbut-3-ene-1, 2-diyl dibenzoate

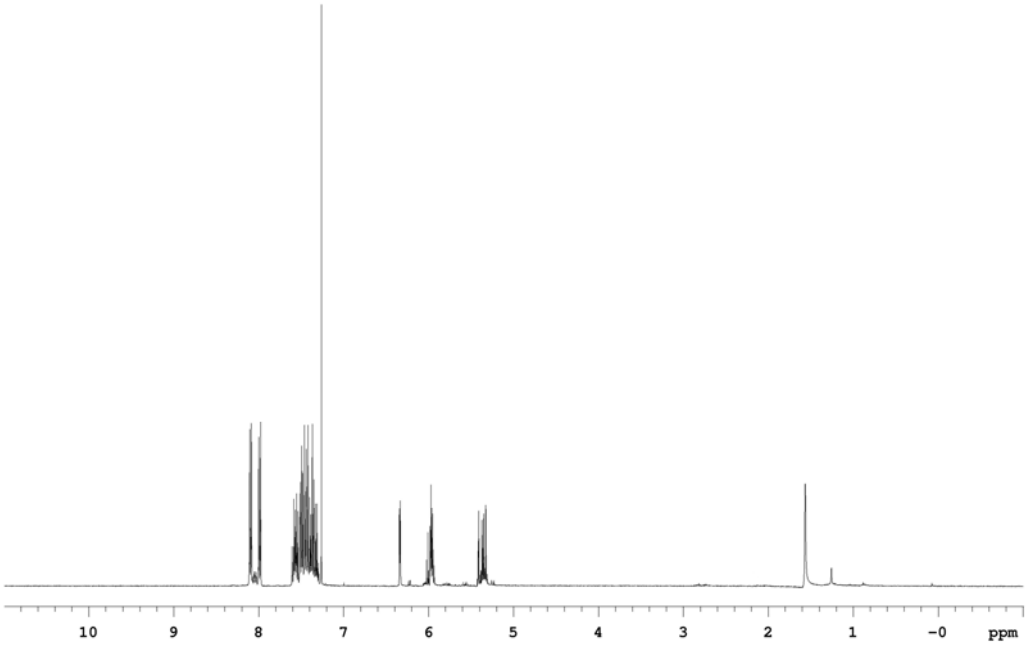


3.12a

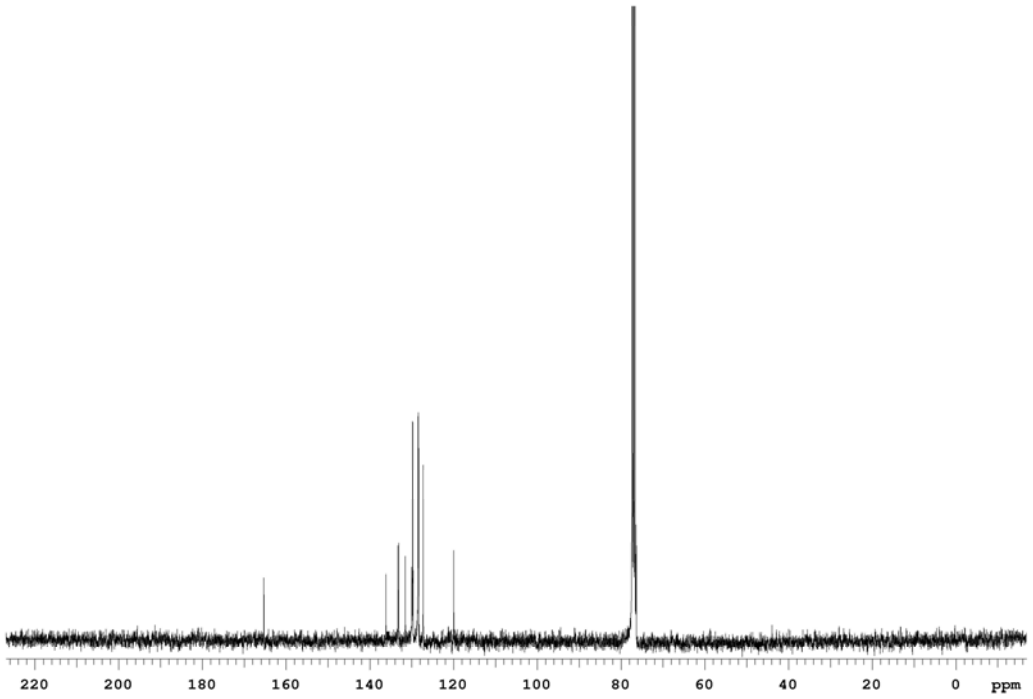
^1H NMR (400 MHz, $CDCl_3$): δ 8.11-8.08 (m, 2H), 8.00-7.98 (m, 2H), 7.60-7.26 (m, 11H), 6.34 (d, *J* = 4.4 Hz, 1H), 6.02-5.93 (m, 2H), 5.42-5.31 (m, 2H). ^{13}C NMR (100

MHz, $CDCl_3$): δ 165.3, 136.1, 133.2, 133.1, 131.5, 129.9, 129.8, 129.7, 129.6, 128.5, 128.4, 128.3, 128.2, 127.2, 119.9, 76.4, 76.3. HPLC: (Chiralcel OJ-H + OJ-H columns, hexanes:*i*-PrOH = 93:7, 0.5 mL/min, 230 nm), t_{major} = 47.5 min, t_{minor} = 51.7 min; ee = 99%. $[\alpha]_D^{25}$= -7.30 (c =1.31, CH_2Cl_2). FTIR (neat): 1711, 1601, 1451, 1314, 1264, 1176, 1106, 1068, 1026, 989, 964, 932, 858, 763, 736, 704, 685 cm^{-1}. HRMS (CI) Calcd. for $C_{24}H_{21}O_4$ $[M+H]^+$: 373.1440, Found: 373.1444.

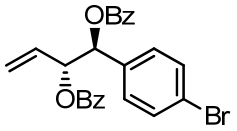
^{1}H NMR



^{13}C NMR



(1*S*, 2*R*)-1-(4-bromophenyl)but-3-ene-1, 2-diyl dibenzoate

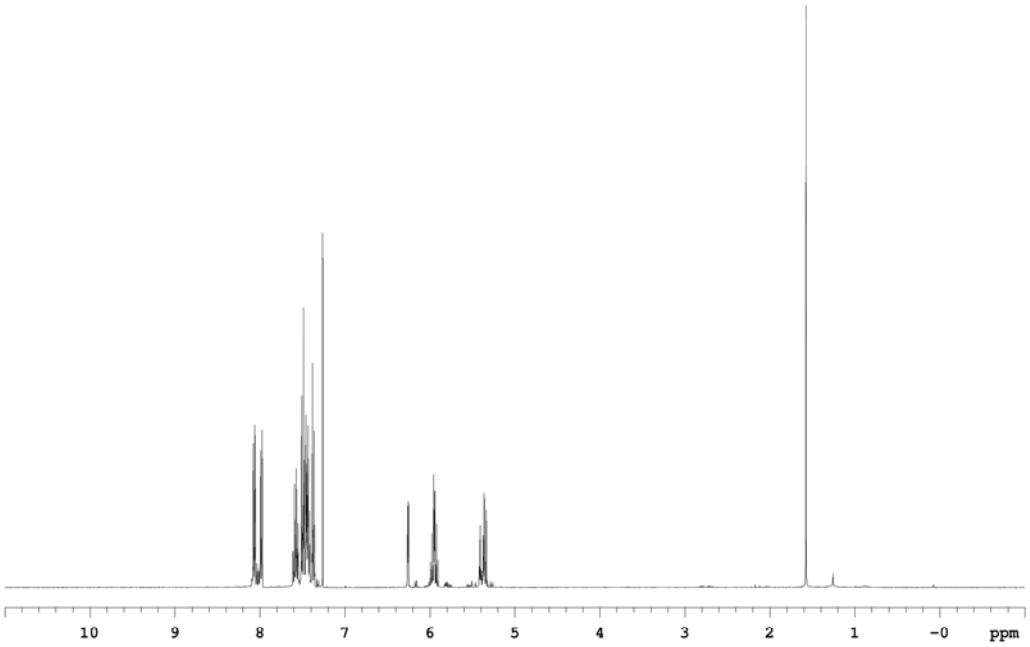


3.12b

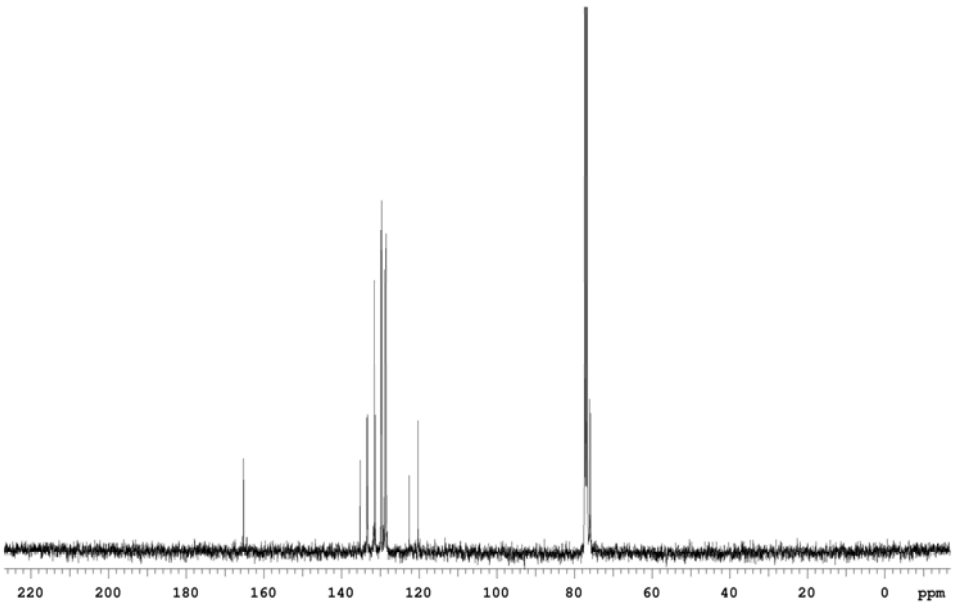
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.05 (m, 2H), 8.00-7.97 (m, 2H), 7.61-7.55 (m, 2H), 7.51-7.42 (m, 6H), 7.39-7.26 (m, 2H), 6.26 (d, *J* = 4.0 Hz, 1H), 6.00-5.90 (m, 2H), 5.42-5.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 165.1, 135.2, 133.4, 133.3, 131.5, 131.3, 129.8, 129.7, 129.6, 129.0, 128.5, 128.4, 122.5, 120.3, 76.0, 75.8. HPLC: (Chiralcel AD-H + OD-H columns, hexanes:*i*-PrOH = 96:4, 0.5 mL/min, 230 nm), t_{major} = 38.4 min, t_{minor} = 46.1 min; ee = 90%. $[\alpha]_D^{25}$= -7.5 (c =1.73, CH_2Cl_2). FTIR (neat): 1721,

1602, 1489, 1451, 1315, 1264, 1177, 1107, 1096, 1070, 1026, 1012, 987, 938, 895, 830, 734, 709 cm^{-1}. HRMS (CI) Calcd. for $C_{24}H_{20}O_4Br$ $[M+H]^+$: 451.0545, Found: 451.0555.

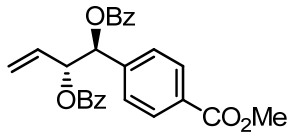
^1H NMR



^{13}C NMR



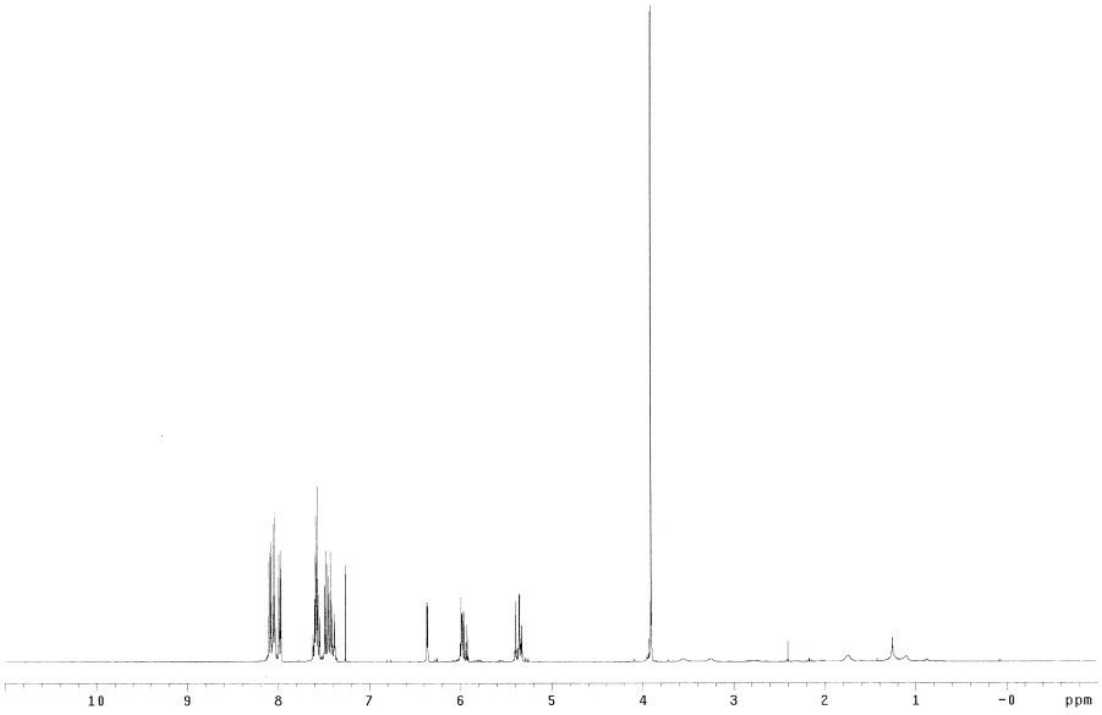
(1*S*, 2*R*)-1-(4-(methoxycarbonyl)phenyl)but-3-ene-1, 2-diyl dibenzoate



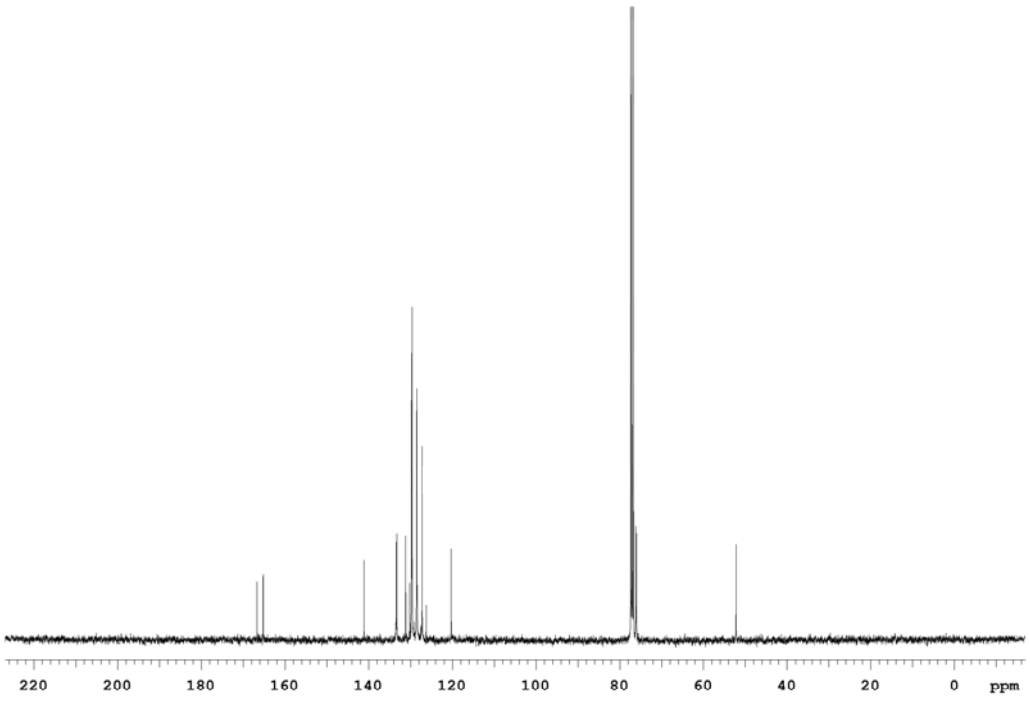
3.12c

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.03 (m, 4H), 8.00-7.97 (m, 2H), 7.62-7.54 (m, 4H), 7.49-7.37 (m, 4H), 6.37 (d, *J* = 4.0 Hz, 1H), 6.00-5.92 (m, 2H), 5.41-5.32 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 165.2, 165.1, 141.1, 133.4, 133.3, 131.1, 130.2, 129.8, 129.7, 129.6, 128.5, 128.4, 128.3, 127.2, 126.2, 120.3, 76.1, 76.0, 52.2. HPLC: (Chiralcel OJ-H + OD-H columns, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 230 nm), t_{major} = 47.7 min, t_{minor} = 52.9 min; ee = 99%. $[\alpha]_D^{25}$= +4.05 (c =1.42, CH_2Cl_2). FTIR (neat): 1719, 1601, 1451, 1436, 1314, 1263, 1178, 1106, 1069, 1026, 987, 937, 855, 803, 772, 733, 708 cm^{-1}. HRMS (CI) Calcd. for $C_{26}H_{23}O_6$ $[M+H]^+$: 413.1495, Found: 431.1497.

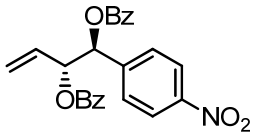
^{1}H NMR



^{13}C NMR



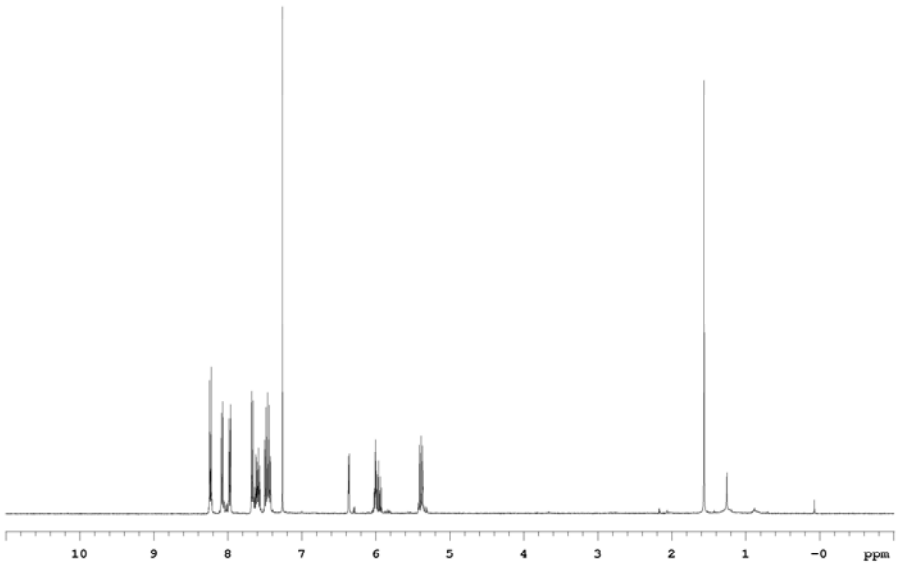
(1*S*, 2*R*)-1-(4-nitrophenyl)but-3-ene-1, 2-diyl dibenzoate



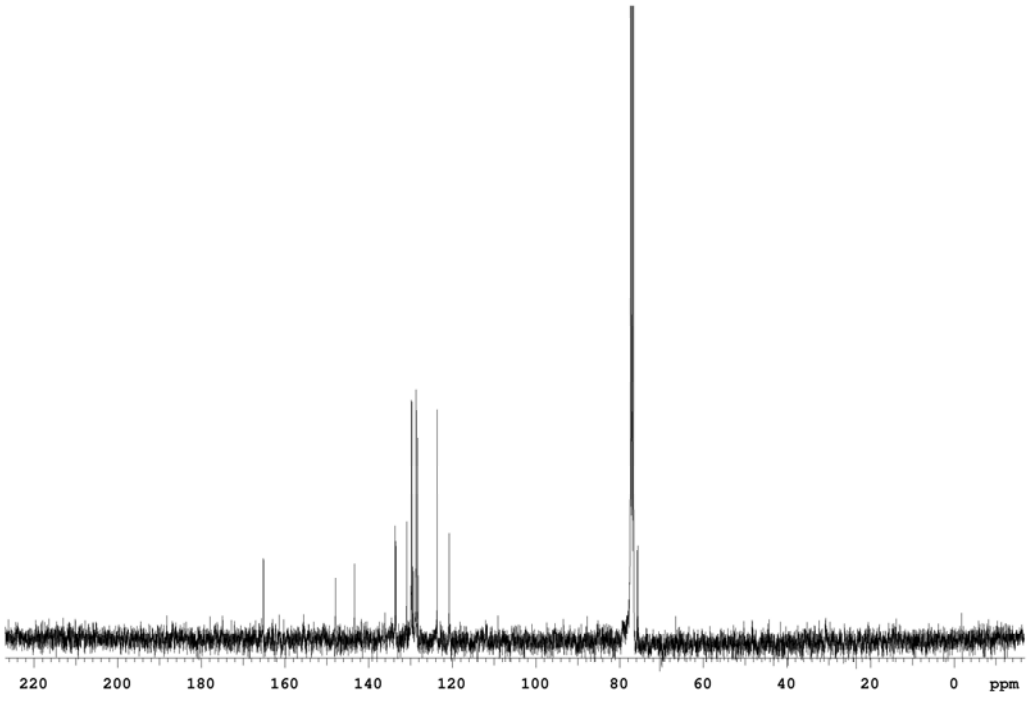
3.12d

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.22 (m, 2H), 8.09-8.06 (m, 2H), 7.99-7.96 (m, 2H), 7.68-7.66 (m, 2H), 7.62-7.56 (m, 2H), 7.50-7.42 (m, 4H), 6.36 (d, *J* = 4.4 Hz, 1H), 6.02-5.92 (m, 2H), 5.41-5.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 147.9, 143.3, 133.7, 133.5, 130.9, 129.8, 129.6, 129.4, 129.2, 128.7, 128.6, 128.2, 123.6, 120.7, 75.8, 75.6. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{minor} = 35.7 min, t_{major} = 44.1 min; ee = 99%. $[\alpha]_D^{25}$= -25.3 (c =0.75, CH_2Cl_2). FTIR (neat): 1721, 1602, 1522, 1451, 1347, 1315, 1262, 1177, 1095, 1069, 1026, 987, 937, 855, 709 cm^{-1}. HRMS (CI) Calcd. for $C_{24}H_{20}O_6N$ $[M+H]^+$: 418.1291, Found: 418.1289.

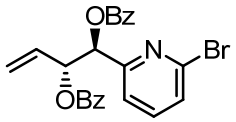
^{1}H NMR



^{13}C NMR



(1*S*, 2*R*)-1-(6-bromopyridin-2-yl)but-3-ene-1, 2-diyl dibenzoate

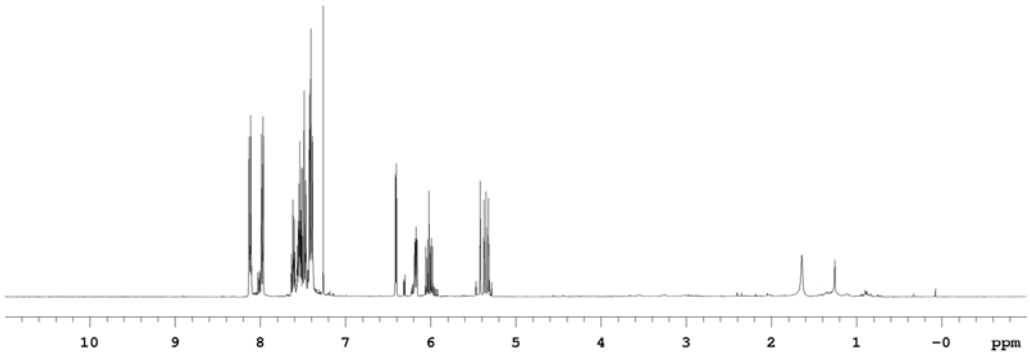


3.12e

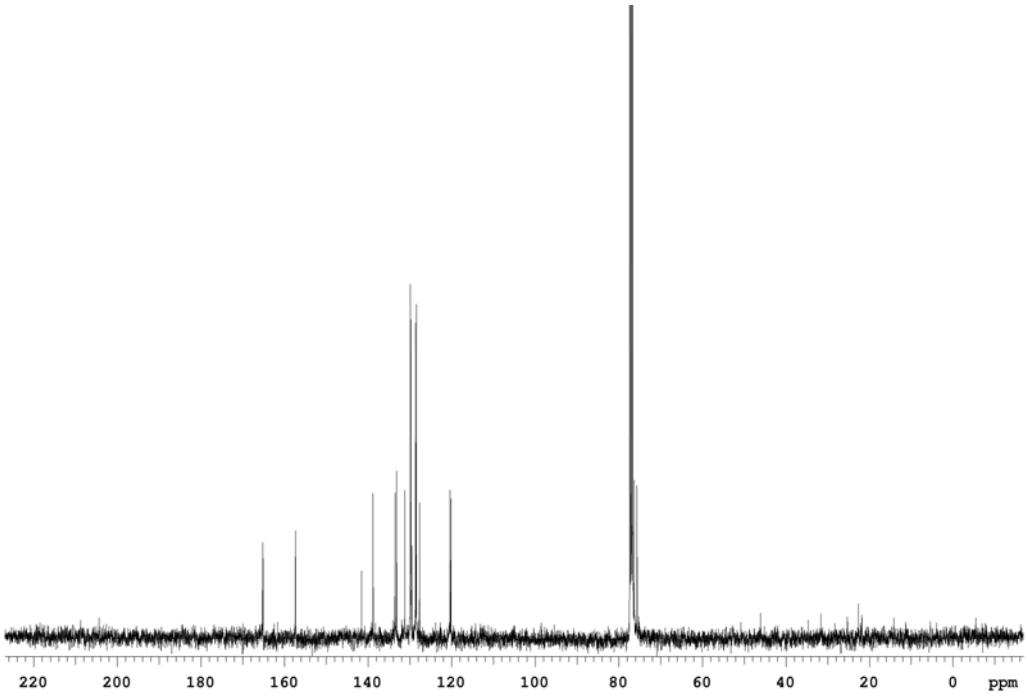
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.10 (m, 2H), 7.99-7.97 (m, 2H), 7.63-7.60 (m, 1H), 7.57-7.47 (m, 4H), 7.43-7.38 (m, 4H), 6.41 (d, *J* = 4.8 Hz, 1H), 6.19-6.16 (m, 1H), 6.06-5.98 (m, 1H), 5.42-5.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 165.1, 157.4, 141.5, 138.8, 133.5, 133.1, 131.2, 129.9, 129.8, 129.7, 129.4, 128.6, 128.4, 127.7, 120.3, 120.1, 76.3, 75.6. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min,

230 nm), t_{major} = 20.4 min, t_{minor} = 33.5 min; ee = 99%. $[\alpha]_D^{25}$= +1.96 (c =1.53, CH_2Cl_2). FTIR (neat): 1721, 1601, 1582, 1558, 1451, 1436, 1409, 1315, 1263, 1177, 1157, 1105, 1094, 1069, 1026, 986, 937, 795, 735, 708, 687, 670 cm^{-1}. HRMS (CI) Calcd. for $C_{23}H_{19}NO_4Br$ $[M+H]^+$: 452.0497, Found: 452.0501.

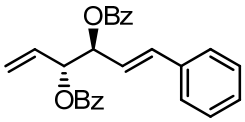
^{1}H NMR



^{13}C NMR



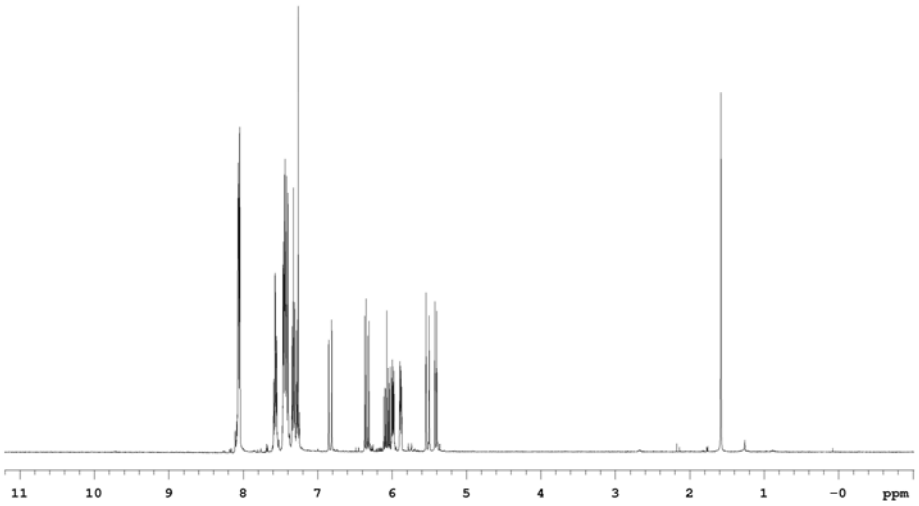
(3*S*, 4*R*, *E*)-1-phenylhexa-1,5-diene-3, 4-diyl dibenzoate



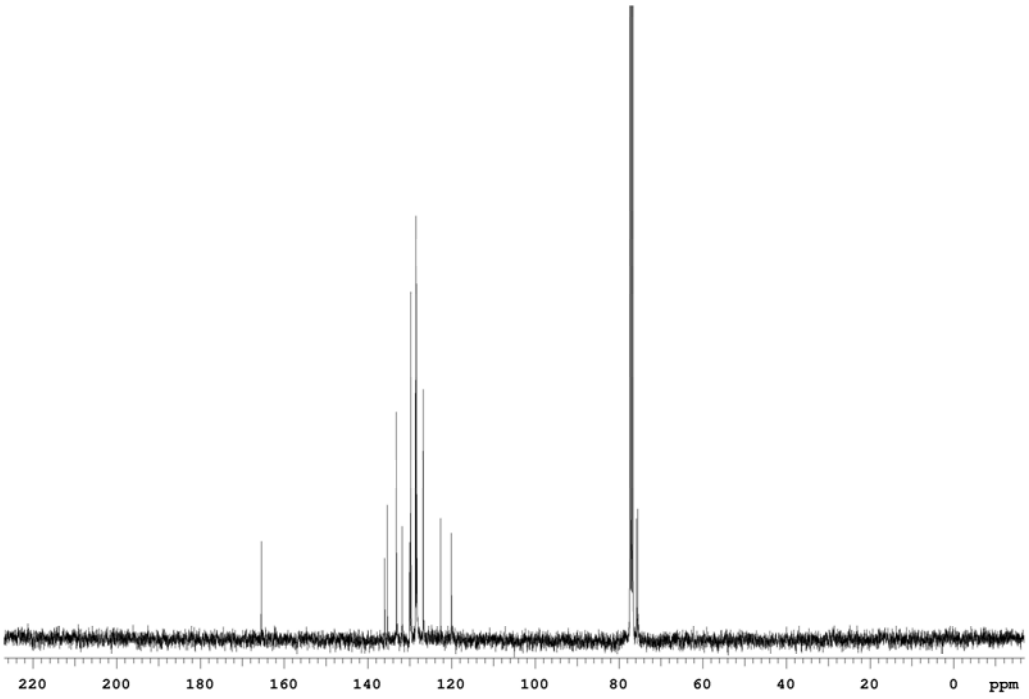
3.12f

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07-8.04 (m, 4H), 7.59-7.55 (m, 2H), 7.47-7.40 (m, 6H), 7.35-7.26 (m, 3H), 6.83 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 17.2, 7.6 Hz, 1H), 6.11-6.03 (m, 1H), 6.00-5.97 (m, 1H), 5.90-5.87 (m, 1H), 5.52 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.41 (dt, *J* = 10.4, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 135.9, 135.3, 133.2, 131.8, 130.0, 129.9, 129.7, 128.6, 128.4, 128.3, 126.8, 122.6, 120.0, 75.8, 75.5. HPLC: (Chiralcel OD-H + OD-H columns, hexanes:*i*-PrOH = 95:5, 0.3 mL/min, 254 nm), t_{minor} = 39.4 min, t_{major} = 40.7 min; ee = 94%. $[\alpha]_D^{25}$= +14.26 (c =2.23, CH_2Cl_2). FTIR (neat): 1720, 1602, 1451, 1315, 1264, 1177, 1108, 1069, 1026, 967, 734, 708 cm^{-1}. HRMS (CI) Calcd. for $C_{26}H_{23}O_4$ $[M+H]^+$: 399.1596, Found: 399.1593.

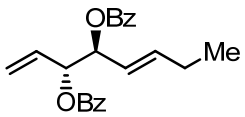
^{1}H NMR



^{13}C NMR



(3*R*, 4*S*, *E*)-octa-1,5-diene-3,4-diyl dibenzoate

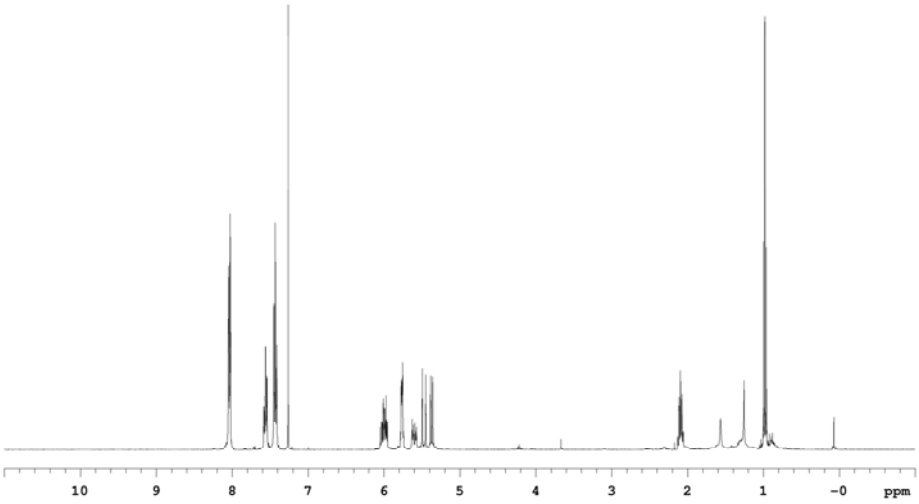


3.12g

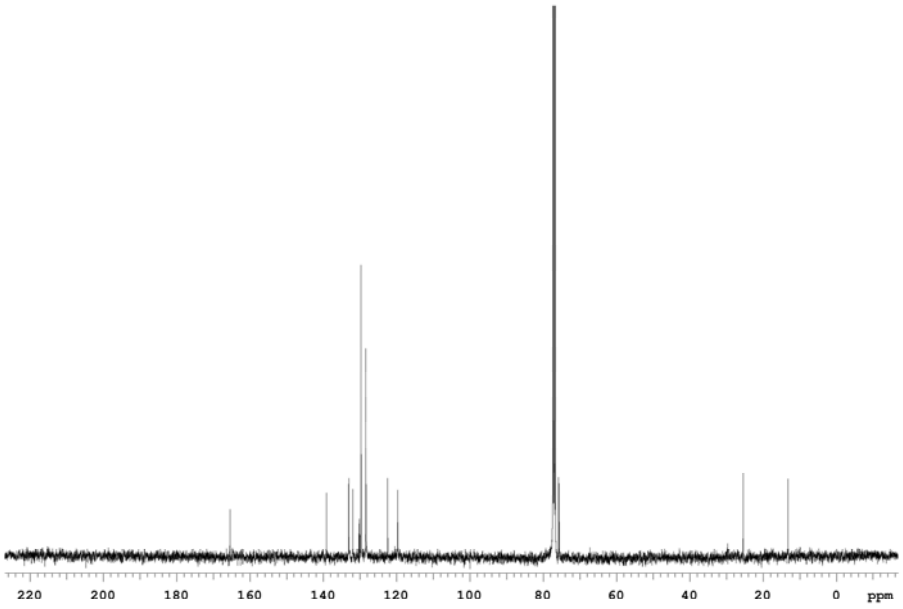
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.02 (m, 4H), 7.58-7.54 (m, 2H), 7.45-7.41 (m, 4H), 6.05-5.96 (m, 2H), 5.78-5.74 (m, 2H), 5.63-5.57 (m, 1H), 5.47 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.37 (dt, *J* = 10.4, 1.2 Hz, 1H), 2.13-2.06 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 139.1, 133.1, 133.0, 131.9, 130.2, 130.1, 129.7, 128.4, 122.4, 119.7, 75.8, 75.6, 25.4, 13.1. HPLC: (Chiralcel AD-H + AD-H columns,

hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 230 nm), t_{major} = 35.3 min, t_{minor} = 37.6 min; ee = 98%. $[\alpha]_D^{25}$= +9.0 (c =2.00, CH_2Cl_2). FTIR (neat): 1720, 1452, 1315, 1264, 1212, 1175, 1109, 1070, 1039, 1026, 970, 734, 705 cm^{-1}. HRMS (CI) Calcd. for $C_{22}H_{23}O_4$ $[M+H]^+$: 351.1596, Found: 351.1599.

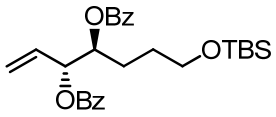
^{1}H NMR



^{13}C NMR



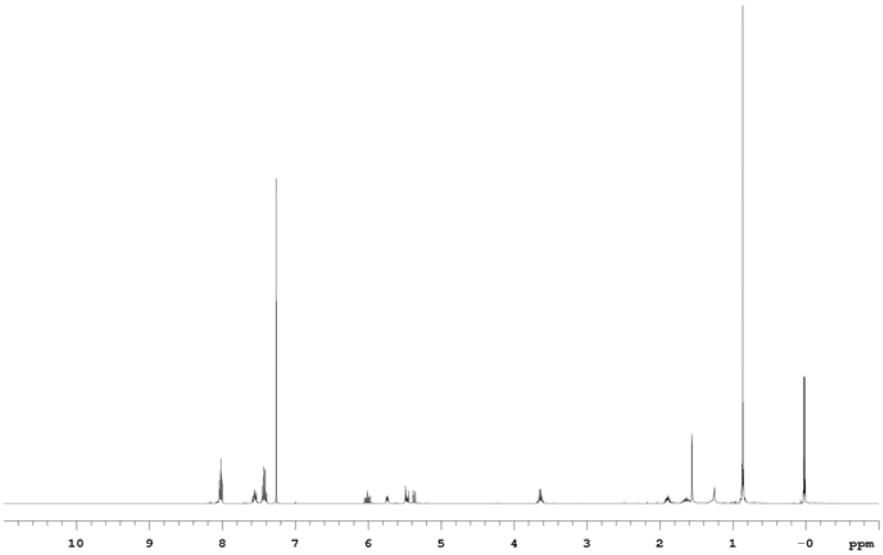
(3*R*, 4*S*)-7-(tert-butyldimethylsilyloxy)hept-1-ene-3,4-diyl dibenzoate



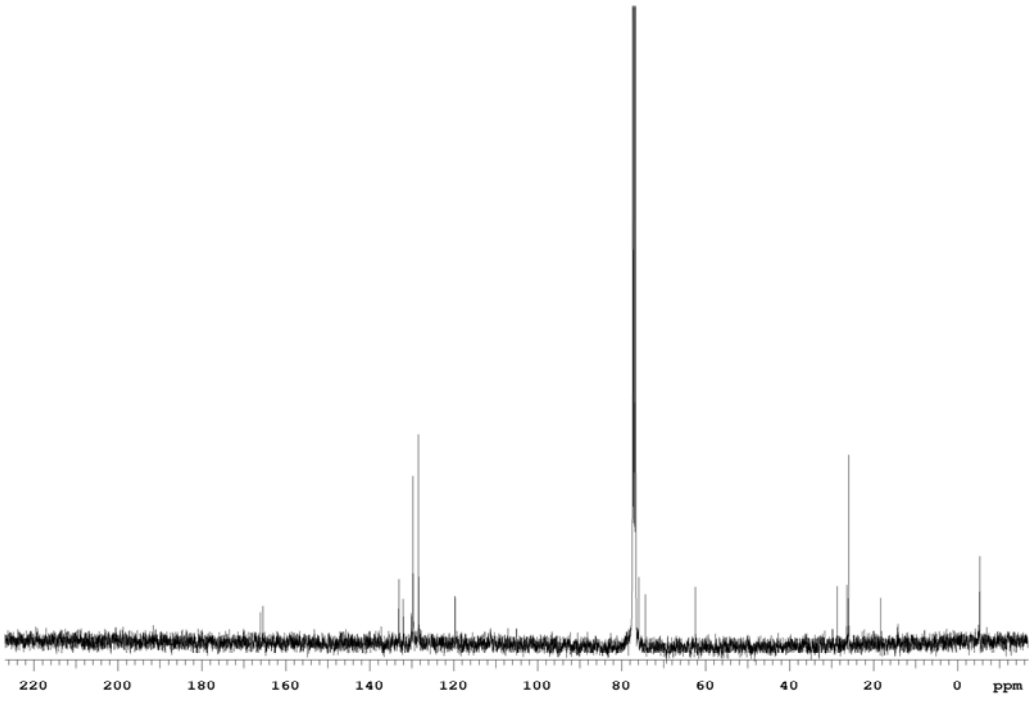
3.12h

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-8.00 (m, 4H), 7.58-7.53 (m, 2H), 7.45-7.39 (m, 4H), 6.05-5.97 (m, 1H), 5.75-5.72 (m, 1H), 5.50-5.45 (m, 2H), 5.37 (dt, *J* = 10.4, 1.2 Hz, 1H), 3.69-3.59 (m, 2H), 1.93-1.86 (m, 2H), 1.66-1.56 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 165.4, 133.0, 132.0, 130.1, 129.7, 128.4, 119.7, 75.9, 74.3, 62.4, 28.6, 26.3, 25.9, 18.3, -5.3. HPLC: (Chiralcel AD-H + AD-H columns, hexanes:*i*-PrOH = 99.5:0.5, 0.3 mL/min, 230 nm), t_{major} = 43.9 min, t_{minor} = 51.9 min; ee = 94%. $[\alpha]_D^{25}$= +6.93 (c =2.02, CH_2Cl_2). FTIR (neat): 1717, 1451, 1315, 1273, 1247, 1177, 1097, 1059, 1024, 949, 834, 776, 737, 708, 687 cm^{-1}. HRMS (CI) Calcd. for $C_{27}H_{37}O_5Si$ $[M+H]^+$: 469.2410, Found: 469.2419.

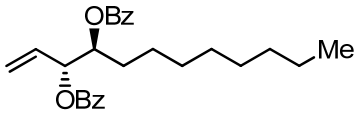
^{1}H NMR



^{13}C NMR



(3*R*, 4*S*)-dodec-1-ene-3, 4-diyl dibenzoate

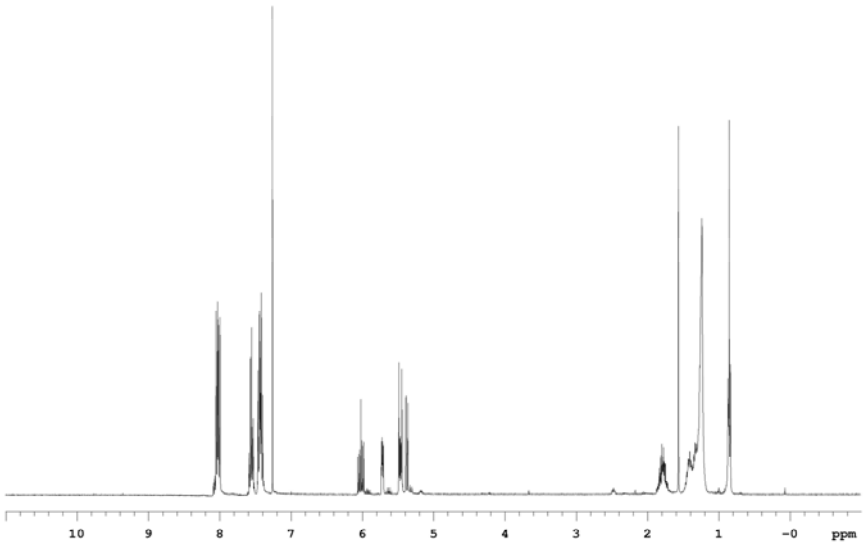


3.12i

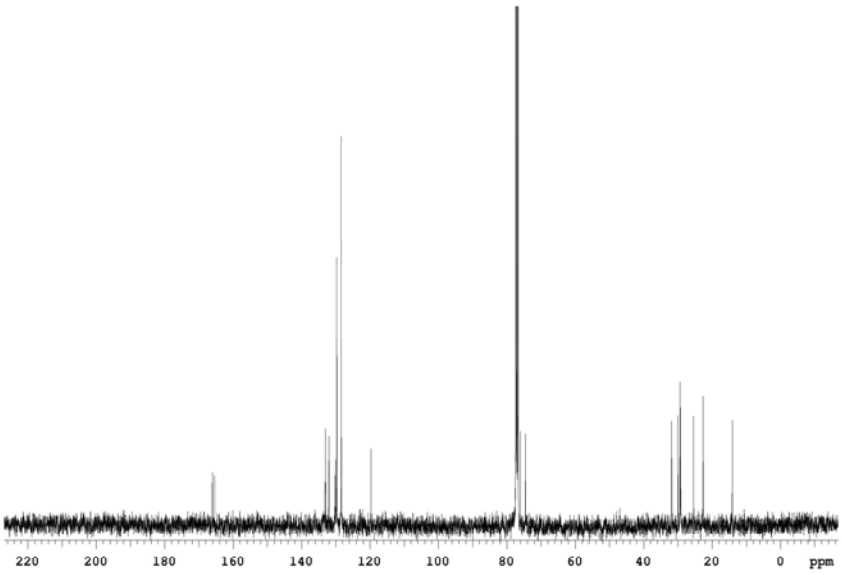
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.00 (m, 4H), 7.59-7.53 (m, 2H), 7.47-7.40 (m, 4H), 6.07-5.98 (m, 1H), 5.73-5.70 (m, 1H), 5.49-5.45 (m, 2H), 5.37 (dt, *J* = 10.4, 1.2 Hz, 1H), 1.84-1.74 (m, 2H), 1.45-1.24 (m, 12H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 165.4, 133.0, 132.9, 132.0, 130.2, 130.1, 130.0, 128.4, 119.7, 75.9, 74.5, 31.8, 30.0, 29.4, 29.3, 29.2, 25.4, 22.6, 14.1. HPLC: (Chiralcel AD-H + OD-H columns,

hexanes:*i*-PrOH = 99:1, 0.3 mL/min, 230 nm), t_{major} = 39.3 min, t_{minor} = 42.4 min; ee = 97%. $[\alpha]_D^{25}$= +8.47 (c =1.77, CH_2Cl_2). FTIR (neat): 1721, 1602, 1452, 1315, 1264, 1177, 1108, 1080, 1060, 1024, 949, 802, 736, 708, 687 cm^{-1}. HRMS (CI) Calcd. for $C_{26}H_{33}O_4$ $[M+H]^+$: 409.2379, Found: 409.2379.

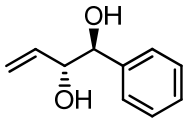
^{1}H NMR



^{13}C NMR



(1*S*,2*R*)-1-phenylbut-3-ene-1, 2-diol



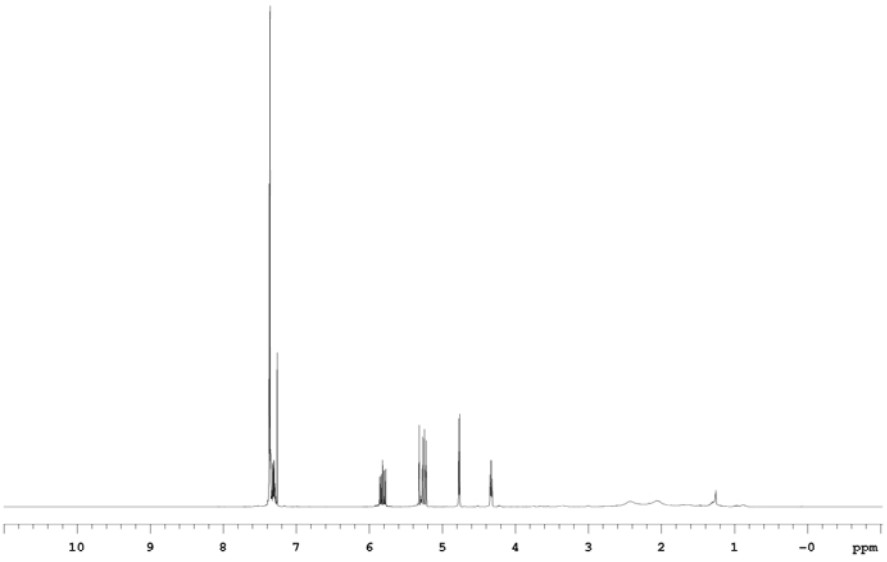
3.13a

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with ***(R)-SEGPHOS*-I** (10.3 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Benzaldehyde **3.11a** (21 mg, 0.2 mmol, 100 mol%), acrolein *gem*-dibenzoate **3.10e** (113 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. K_2CO_3 (55 mg, 0.4 mmol, 200 mol%) and MeOH (2.0 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 18 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:10) provided **3.13a** (25 mg, 0.154 mmol) as a colorless oil in 77% yield (17:1 dr).

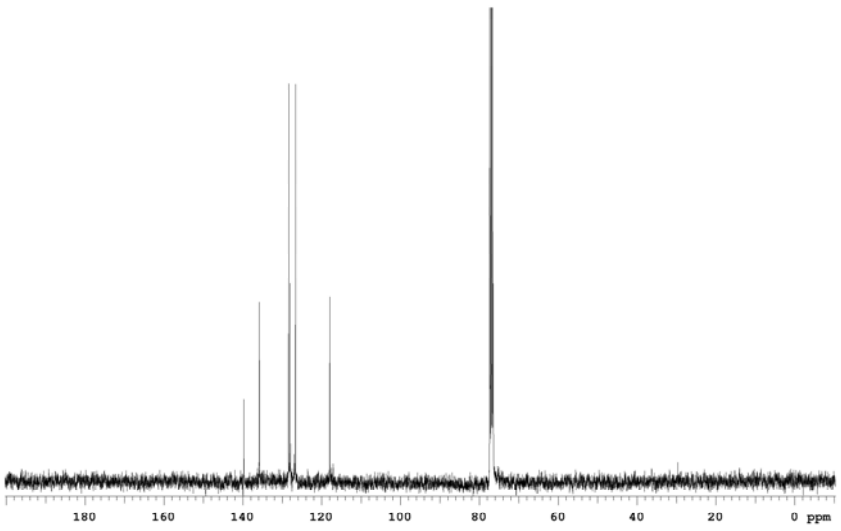
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 5H), 5.89-5.74 (m, 1H), 5.38-5.22 (m, 2H), 4.77 (d, *J* = 4.4 Hz, 1H), 4.35-4.31 (m, 1H), 2.46 (br, 1H), 2.08 (br, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 135.8, 128.3, 127.9, 126.6, 117.9, 76.5 (two carbons are overlapped). GC: (Cyclosil-B: initial temperature: 100 ^oC (5 min hold), final temperature: 220 ^oC (2 min hold), rate: 2 ^oC/min): t_{major} = 37.2 min, t_{minor} = 37.5 min; ee = 99%.

$[\alpha]_D^{25}$= +71.0 (c =0.91, $CHCl_3$). (The absolute configuration of the product is determined by correlation with a known compound). FTIR (neat): 3388, 2920, 1494, 1452, 1427, 1197, 1122, 1091, 1063, 1028, 995, 927, 863, 830, 763, 724, 700 cm^{-1}. HRMS (CI) Calcd. for $C_{10}H_{11}O_2$ $[M-H]^+$: 163.0759, Found: 163.0757.

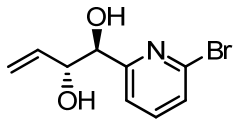
^1H NMR



^{13}C NMR



(1*S*, 2*R*)-1-(6-bromopyridin-2-yl)but-3-ene-1, 2-diol



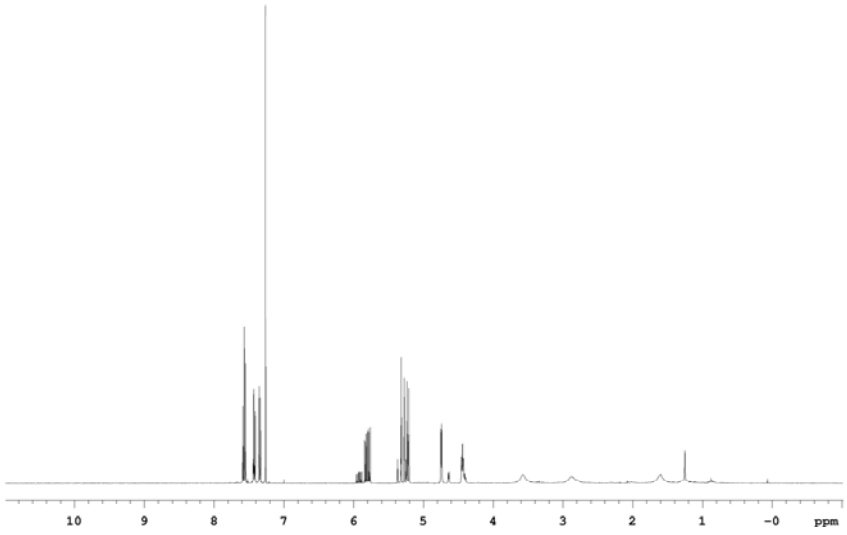
3.13e

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with ***(R)-SEGPHOS*-I** (10.3 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). 6-Bromopyridine-2-carboxaldehyde **3.11e** (37 mg, 0.2 mmol, 100 mol%), acrolein *gem*-dibenzoate **3.10e** (113 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. K_2CO_3 (55 mg, 0.4 mmol, 200 mol%) and MeOH (2.0 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 18 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:10) provided **3.13e** (30 mg, 0.124 mmol) as a colorless oil in 62% yield (7:1 dr).

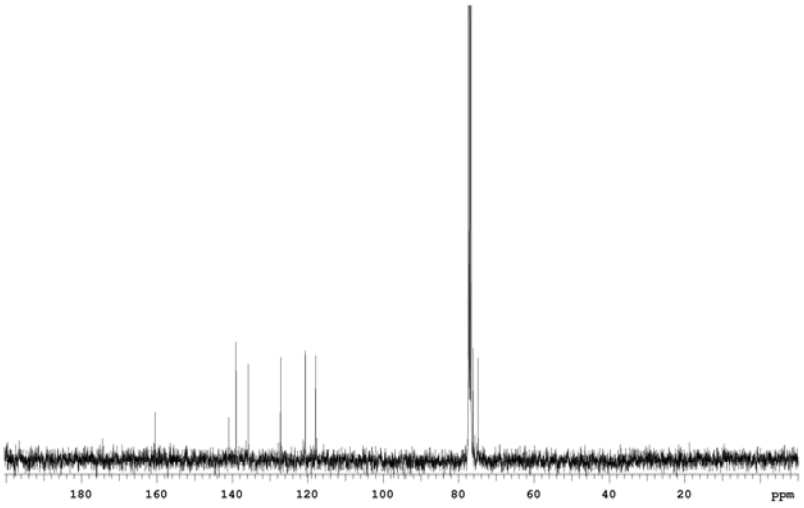
^1H NMR (400 MHz, $CDCl_3$): δ 7.58-7.55 (m, 1H), 7.44-7.41 (m, 1H), 7.36-7.33 (m, 1H), 5.84-5.76 (m, 1H), 5.29 (dt, *J* = 17.6, 1.6 Hz, 1H), 5.22 (dt, *J* = 10.8, 1.6 Hz, 1H), 4.74 (d, *J* = 4.8 Hz, 1H), 4.45-4.23 (m, 1H), 3.57 (br, 1H), 2.87 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 140.9, 139.0, 135.7, 127.2, 120.6, 117.9, 76.1, 74.8. GC: (Cyclosil-B:

initial temperature: 120 ^{o}C (10 min hold), final temperature: 180 ^{o}C (5min hold), rate: 1.5 ^{o}C/min): t_{minor} = 47.7 min, t_{major} = 48.2 min; ee = 96%. $[\alpha]_D^{25}$= +20.8 (c =0.90, CH_2Cl_2). FTIR (neat): 2304, 1557, 1440, 1265, 896, 733, 704 cm^{-1}. HRMS (CI) Calcd. for $C_9H_{11}NO_2Br$ $[M+H]^+$: 243.9973, Found: 243.9975.

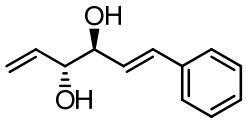
^{1}H NMR



^{13}C NMR



(3*S*, 4*R*, *E*)-1-phenylhexa-1,5-diene-3, 4-diol



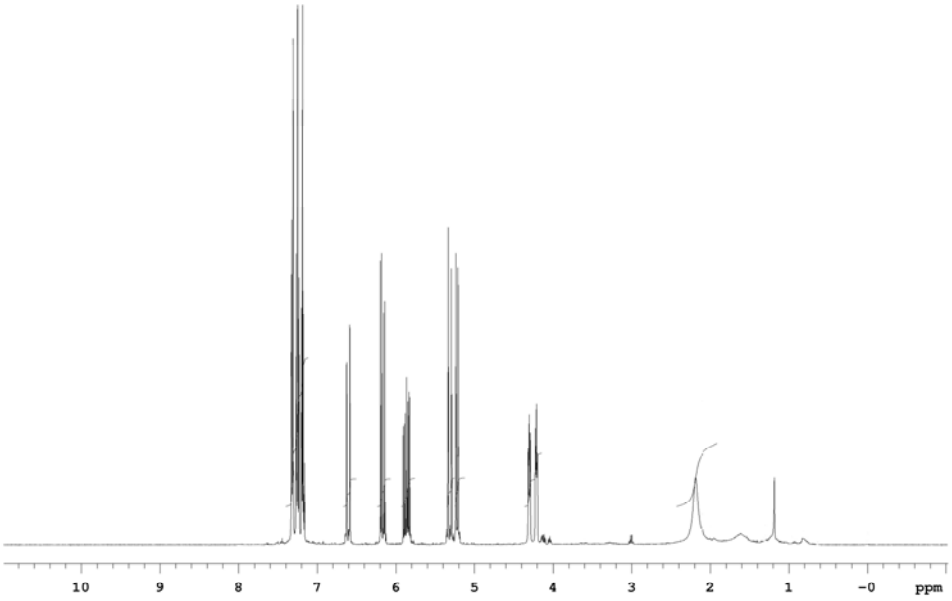
3.13f

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with ***(R)-SEGPHOS*-I** (10.3 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Cinnamaldehyde **3.11f** (26 mg, 0.2 mmol, 100 mol%), acrolein *gem*-dibenzoate **3.10e** (113 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. K_2CO_3 (55 mg, 0.4 mmol, 200 mol%) and MeOH (2.0 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 18 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:10) provided **3.13f** (26 mg, 0.136 mmol) as a colorless oil in 68% yield (18:1 dr).

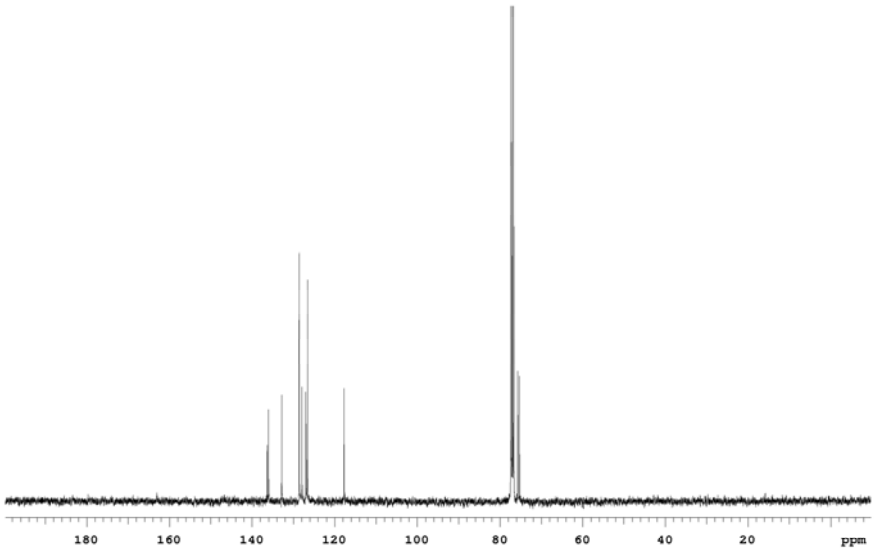
^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.16 (m, 5H), 6.60 (dd, *J* = 16.0, 0.8 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.90-5.82 (m, 1H), 5.31 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.32-4.20 (m, 2H), 2.19 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 136.0, 132.8, 128.6, 127.9, 126.9, 126.6, 117.7, 75.7, 75.3. GC: (Cyclosil-B: initial temperature: 100 ^oC (5 min hold), final temperature: 200 ^oC (5 min hold), rate: 2.5

^{o}C/min): t_{major} = 41.0 min, t_{minor} = 41.3 min; ee = 97%. $[\alpha]_D^{25}$= +15.4 (c =0.80, CH_2Cl_2). FTIR (neat): 3388, 1699, 1494, 1450, 1265, 1026, 993, 969, 931, 734, 702 cm^{-1}. HRMS (CI) Calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1072, Found: 191.1074.

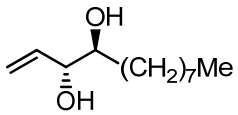
^{1}H NMR



^{13}C NMR



(3*R*, 4*S*)-dodec-1-ene-3,4-diol



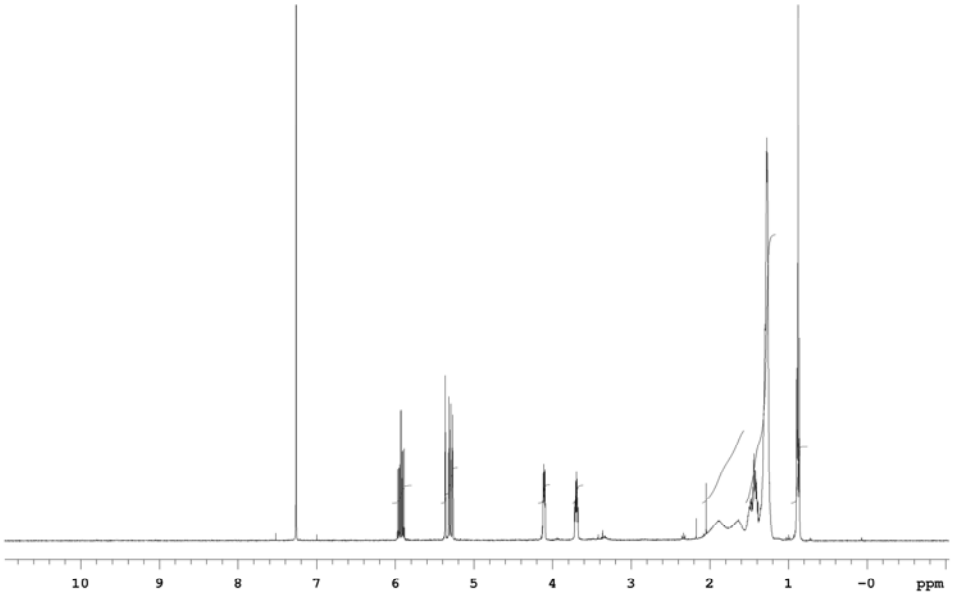
3.13i

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with ***(R)-SEGPHOS*-I** (10.3 mg, 0.01 mmol, 5 mol%) and THF (1.0 M, 0.2 mL). Nonanal **3.11i** (28 mg, 0.2 mmol, 100 mol%), acrolein *gem*-dibenzoate **3.10e** (113 mg, 0.4 mmol, 200 mol%), anhydrous K_3PO_4 (43 mg, 0.2 mmol, 100 mol%) and isopropanol (24 mg, 0.4 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 48 hr, at which point the reaction mixture was cooled to ambient temperature. K_2CO_3 (55 mg, 0.4 mmol, 200 mol%) and MeOH (2.0 mL) were added. The reaction mixture was allowed to stir at ambient temperature for 18 hr, at which point the reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification of the residue by column chromatography (SiO_2; ethyl acetate:hexanes, 1:10) provided **3.13i (**28 mg, 0.14 mmol) as a colorless oil in 70% yield (14:1 dr).

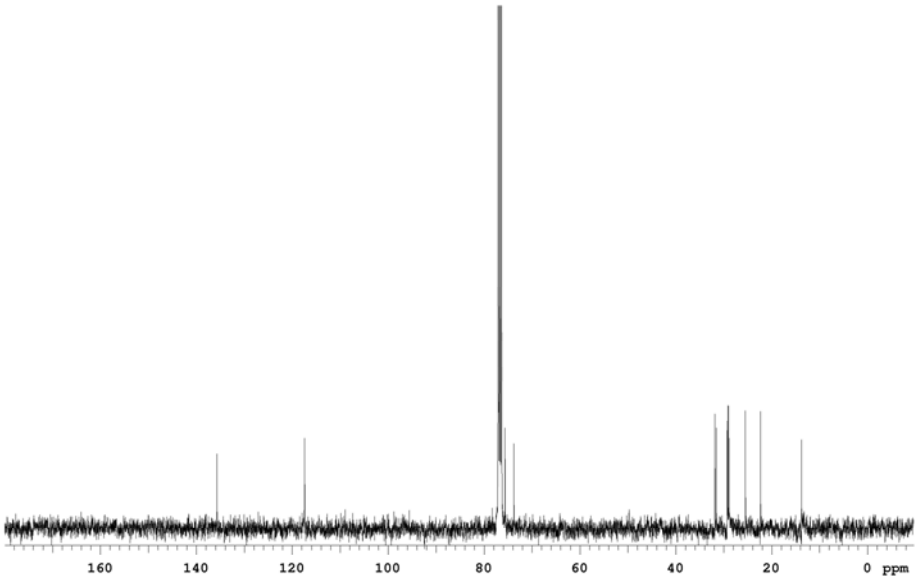
^1H NMR (400 MHz, $CDCl_3$): δ 5.97-5.89 (m, 1H), 5.37-5.27 (m, 2H), 4.12-4.09 (m, 1H), 3.72-3.68 (m, 1H),1.50-1.24 (m, 14H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 117.4, 75.6, 73.7, 31.8, 31.5, 29.3, 29.2, 28.9, 25.5, 22.3, 13.8. GC: (Cyclosil-B: initial temperature: 150 ^oC (5 min hold), final temperature: 200 ^oC (5 min hold), rate: 2.0 ^oC/min): t_{major} = 12.5 min, t_{minor} = 12.8 min; ee = 99%. $[\alpha]_D^{25}$= +7.9 (c =0.65, CH_2Cl_2). FTIR (neat): 3298, 2953, 2917, 2851, 1705, 1467, 1378, 1317, 1264,

1118, 1072, 1028, 1006, 926, 737, 711cm^{-1}. HRMS (CI) Calcd. for $C_{10}H_{11}O_2$ $[M-H]^+$: 199.1698, Found: 199.1695.

^{1}H NMR



^{13}C NMR



Preparation of (*S*)-Ir-Complex I

To a mixture of $[Ir(cod)Cl]_2$ (100 mg, 0.15 mmol, 100 mol%), (*S*)-SEGPHOS (183 mg, 0.3 mmol, 200 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 400 mol%) and *m*-nitrobenzoic acid (100 mg, 0.6 mmol, 400 mol%) in a sealed tube under N_2 atmosphere was added THF (3 mL, 0.05 M). The reaction mixture was heated at 80 ^oC for 30 min and was then allowed to cool to ambient temperature. Allyl acetate (75 mg, 0.75 mmol, 500 mol%) was added and the reaction mixture was allowed to stir for an additional 90 min at 80 ºC, at which point the reaction mixture was allowed to cool to the ambient temperature. The reaction mixture was filtered and washed with THF (15 mL) until all yellow residue was dissolved. The filtrate was concentrated *in vacuo* and hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (233 mg, 0.231 mmol, 77% yield).

The yellow solid was dissolved in THF and diethyl ether was allowed to diffuse into the THF solution at the ambient temperature, resulting in the formation of crystals. Single crystal X-ray diffraction data for (*S*)-Ir-Complex I has been deposited in the CCDB.

General procedure for Enantioselective Carbonyl Reverse Prenylation from the Alcohol Oxidation Level

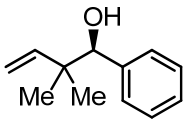
An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with **(*S*)-Ir-complex I** (25 mg, 0.025 mmol, 5 mol%) and toluene (1.0 M, 0.5 mL). Alcohol (0.5 mmol, 100 mol%), 1,1-dimethylallene (68 mg, 1.0 mmol, 200 mol%) and

propionaldehyde (1.5 mg, 0.025 mmol, 5 mol%) were added and the reaction mixture was allowed to stir at 40 ^{o}C for 15 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography provided the corresponding product.

General procedure for Enantioselective Carbonyl Reverse Prenylation from the Aldehyde Oxidation Level

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with **(*S*)-Ir-complex I** (25 mg, 0.025 mmol, 5 mol%) and toluene (1.0 M, 0.5 mL). Aldehyde (0.5 mmol, 100 mol%), 1,1-dimethylallene (68 mg, 1.0 mmol, 200 mol%) and isopropanol (60 mg, 1.0 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 40 ^{o}C for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography provides the corresponding product.

(*R*)-2,2-Dimethyl-1-phenylbut-3-en-1-ol

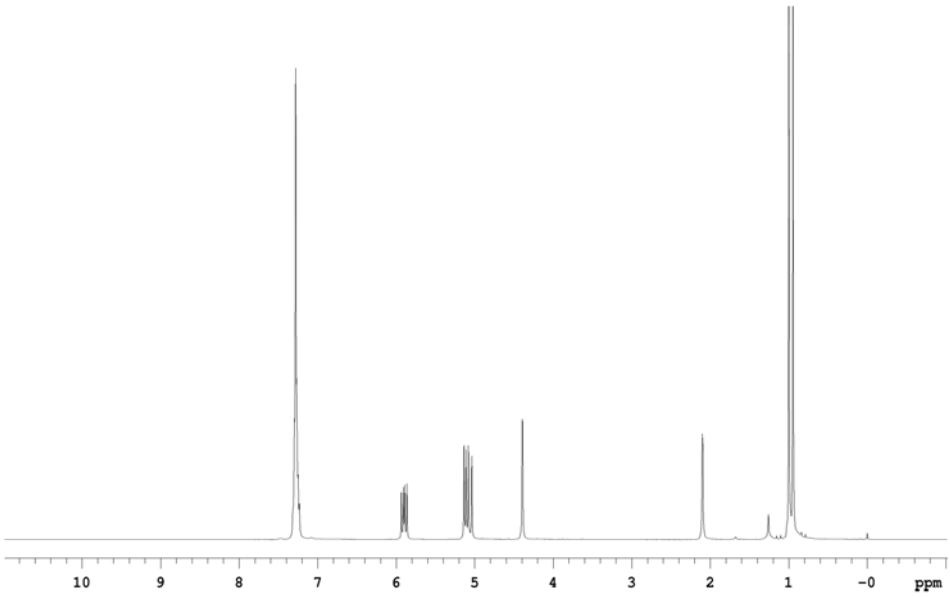


3.16a

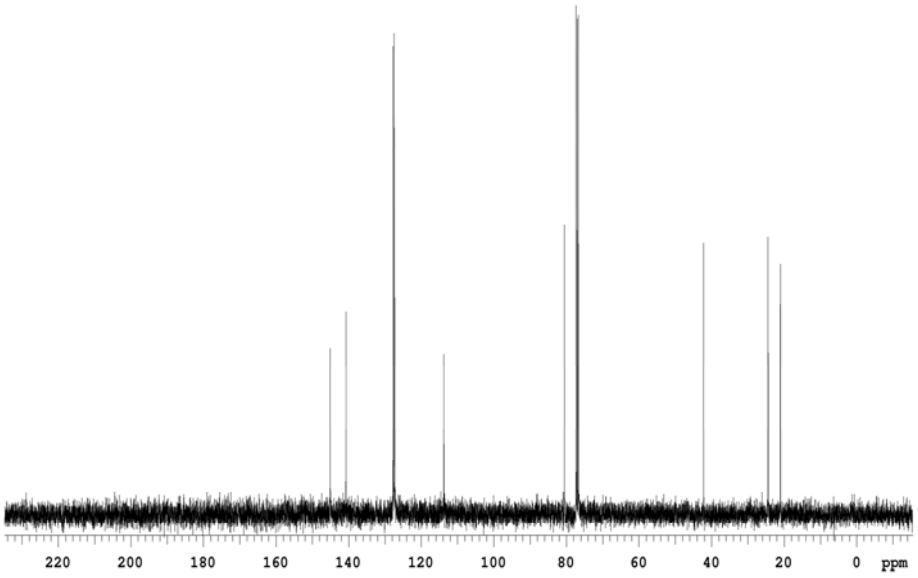
TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 5H), 5.90 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 5.06 (d, *J* = 17.6 Hz, 1H), 4.39 (s, 1H), 2.10 (s, 1H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 145.0, 140.7, 127.7, 127.4, 127.3, 113.8, 80.5, 42.2, 24.4, 21.0. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1 mL/min, 210 nm), t_{minor} = 9.1 min, t_{major} = 11.4 min; ee = 89% (aldehyde), 86% (alcohol).

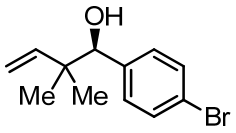
^{1}H NMR



^{13}C NMR



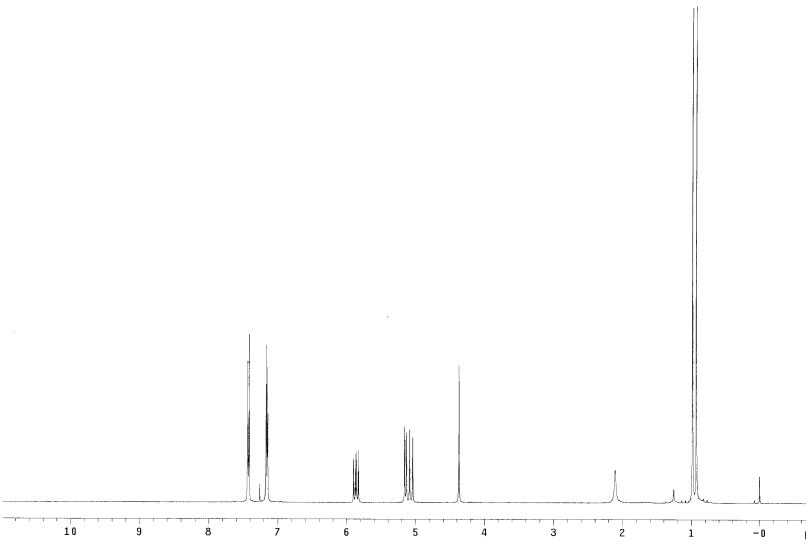
(*R*)-1-(4-Bromophenyl)-2,2-dimethylbut-3-en-1-ol



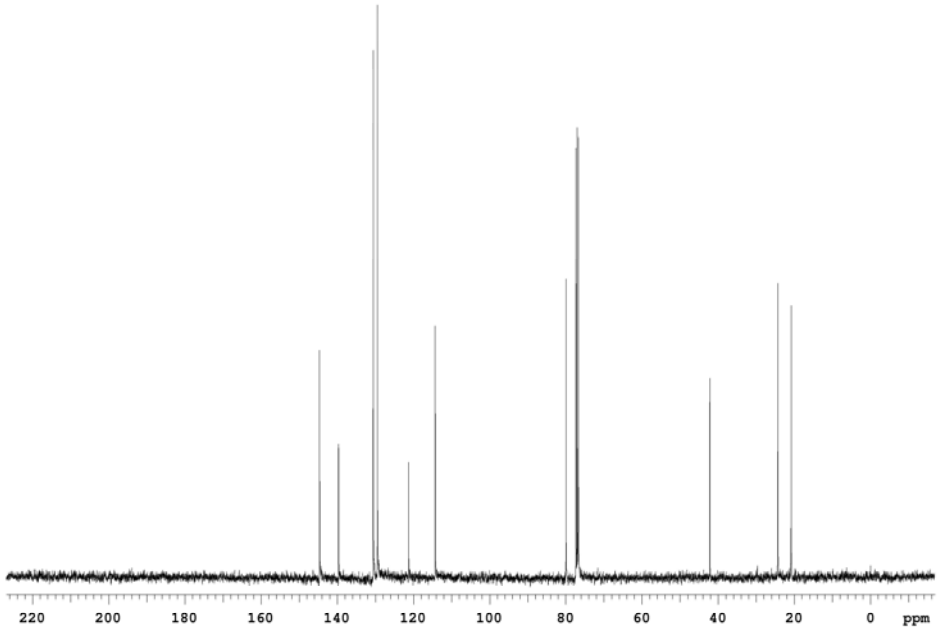
3.16b

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:10). ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.88 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 5.07 (d, *J* = 17.6 Hz, 1H), 4.37 (s, 1H), 2.07 (d, *J* = 2.4 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 139.6, 130.5, 129.4, 121.2, 114.3, 79.9, 42.2, 24.3, 20.8. HRMS (CI) Calcd. for $C_{12}H_{16}OBr$ $(M+H)^+$: 255.0385 Found: 255.0381. FTIR (neat): 3447, 2968, 2871, 1637, 1591, 1487, 1378, 1362, 1284, 1183, 1104, 1070, 1052, 1030, 1009, 915, 884, 836, 817, 754, 694, 670 cm^{-1}.HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 13.9 min, t_{major} = 14.9 min; ee = 90% (aldehyde), 90% (alcohol).

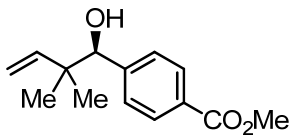
^1H NMR



^{13}C NMR



(*R*)-Methyl 4-(1-hydroxy-2,2-dimethylbut-3-enyl)benzoate

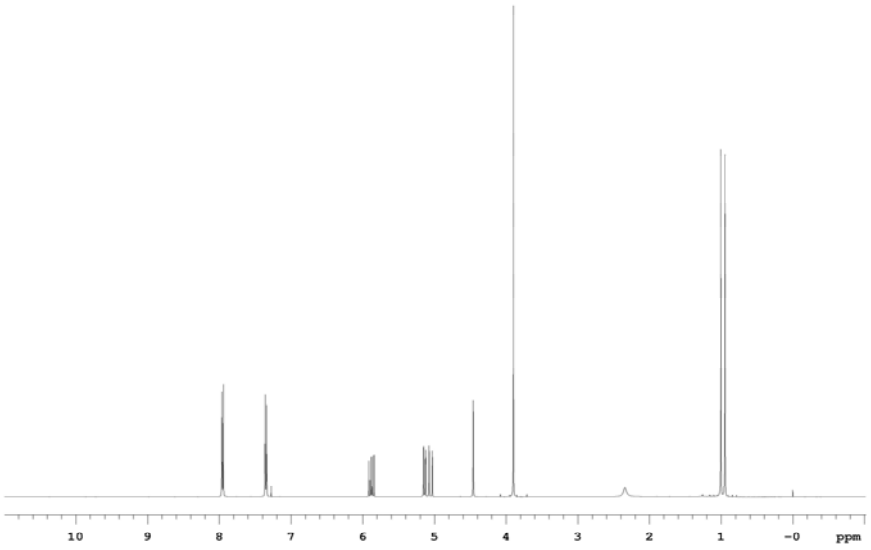


3.16c

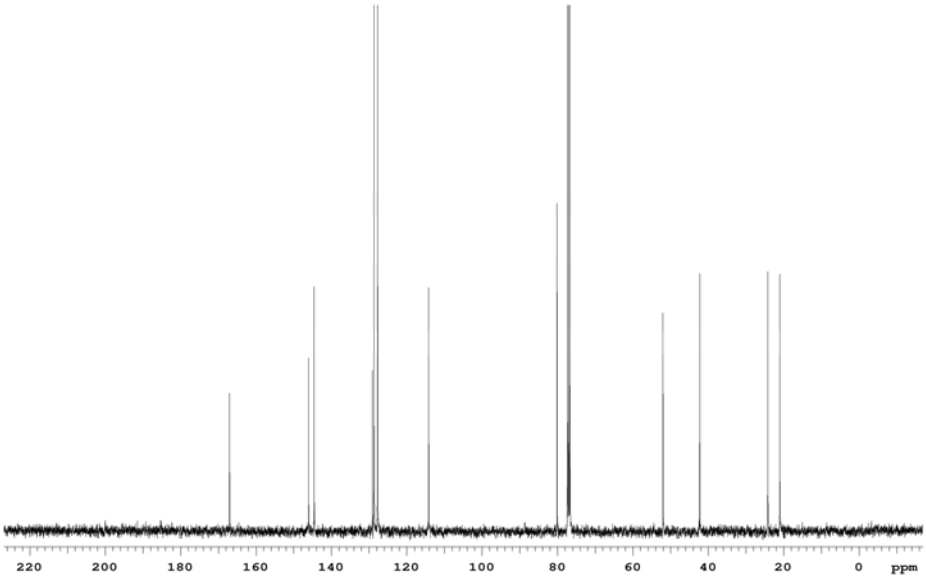
TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 5.88 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.14 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.05 (dd, *J* = 17.6, 1.2 Hz, 1H), 4.46 (s, 1H), 3.90 (s, 3H), 2.34(br, 1H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 146.0, 144.5, 129.1, 128.7, 127.7, 114.2, 80.1, 52.0, 42.2, 24.2, 21.0. HPLC: (Chiralcel OJ-H column,

hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 12.7 min, t_{major} = 17.9 min; ee = 89% (aldehyde), 89% (alcohol).

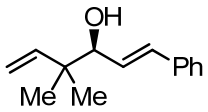
^{1}H NMR



^{13}C NMR



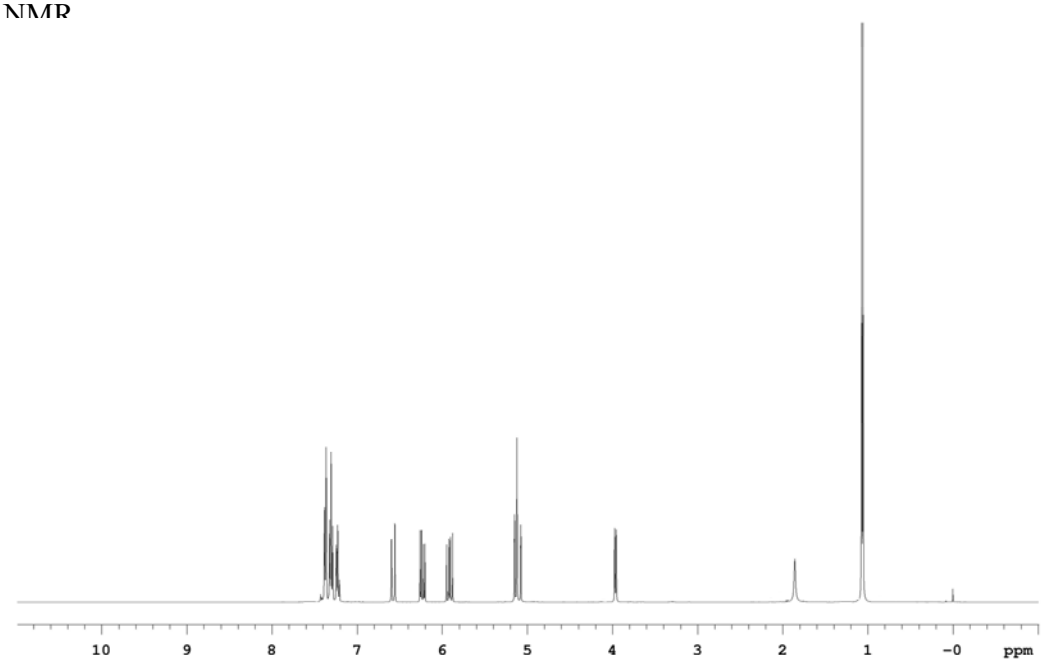
(*S*,*E*)-4,4-Dimethyl-1-phenylhexa-1,5-dien-3-ol



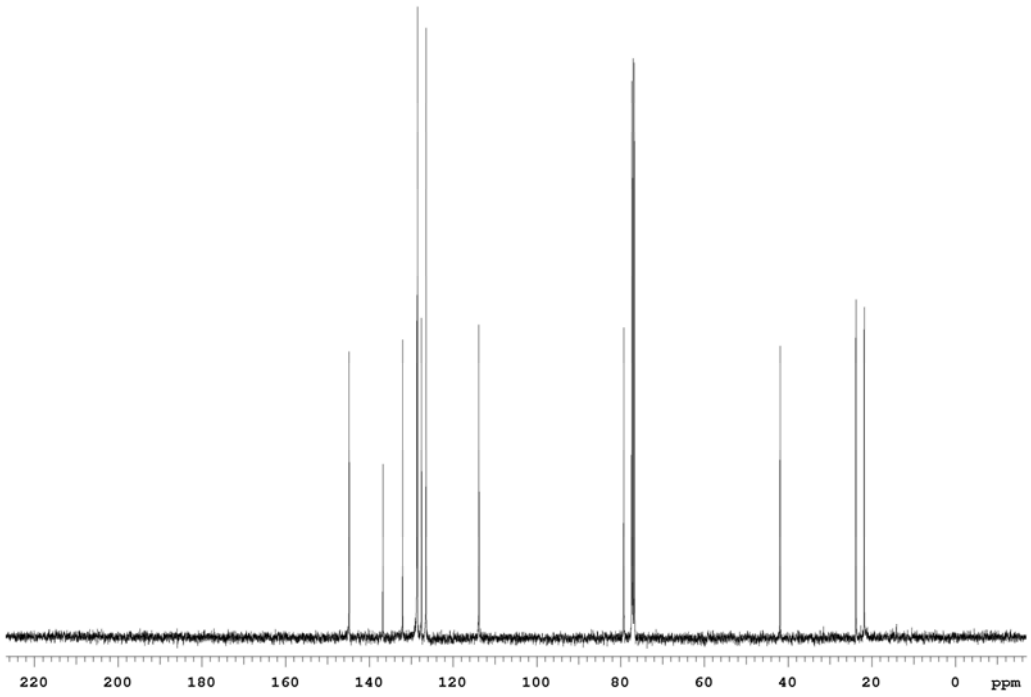
3.16d

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 5H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.91 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.14 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.11 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.97 (dd, *J* = 6.8, 1.2 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 136.8, 132.0, 128.6, 128.5, 127.5, 126.4, 113.8, 79.2, 41.9, 23.8, 21.8. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 254 nm), t_{major} = 13.5 min, t_{minor} = 20.3 min; ee = 93% (aldehyde), 87% (alcohol).

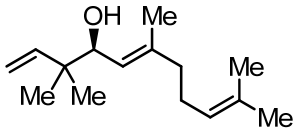
^{1}H NMR



^{13}C NMR



(*S*,*E*)-3,3,6,10-Tetramethylundeca-1,5,9-trien-4-ol

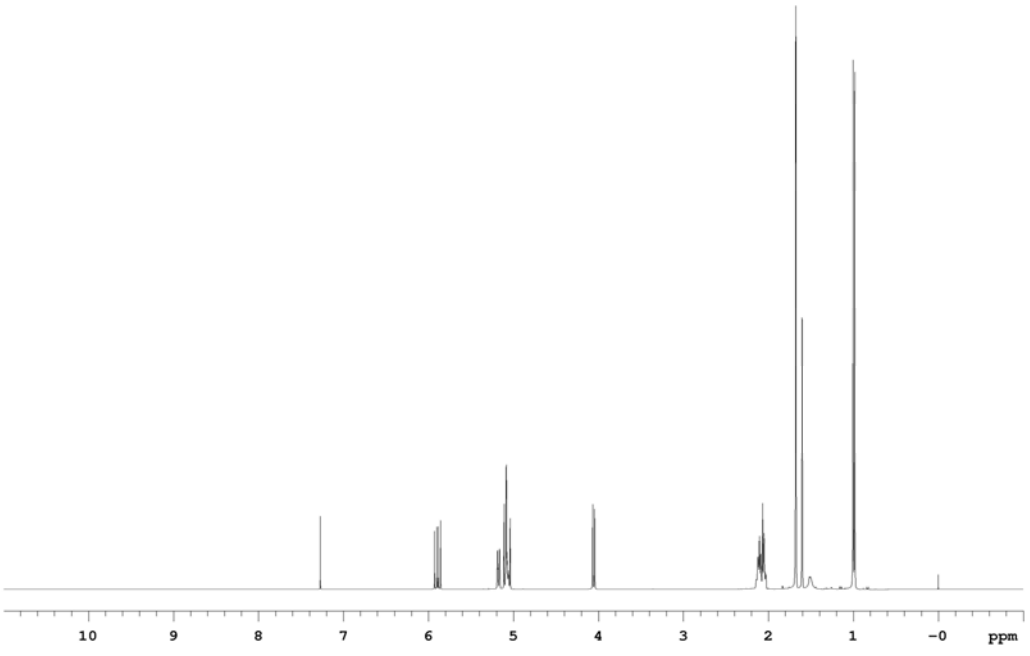


3.16e

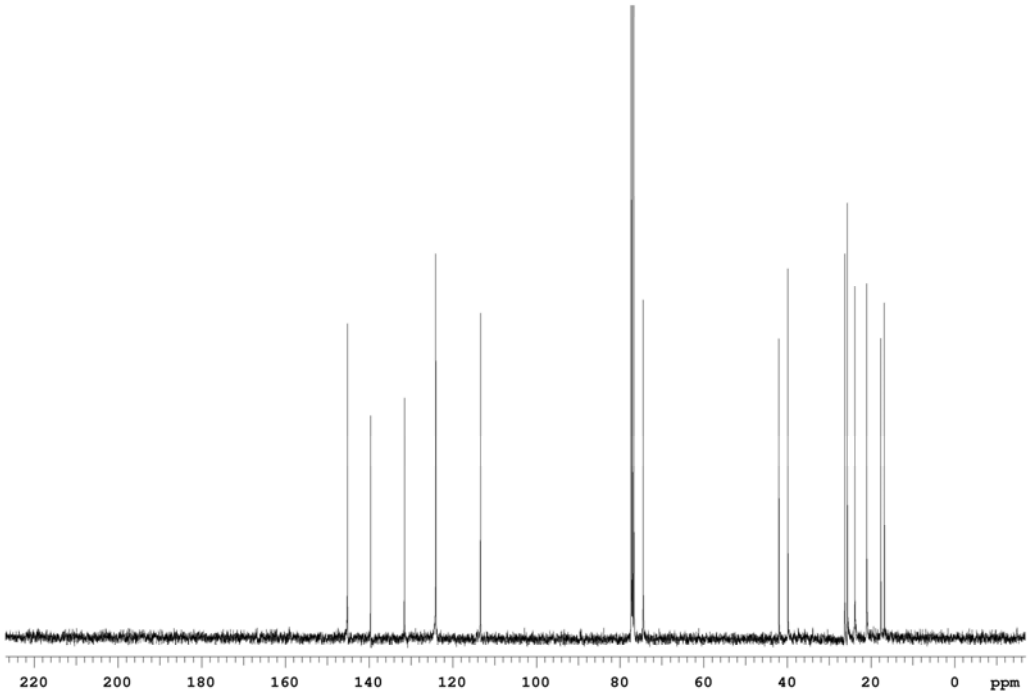
TLC (SiO_2): R_f = 0.37 (ethyl acetate:hexanes, 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.19-5.16 (m, 1H), 5.11-5.04 (m, 1H), 4.06 (d, *J* = 9.6 Hz, 1H), 2.14-2.03 (m, 4H), 1.68 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.52 (br, 1H), 1.00 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 139.6, 131.5, 124.1, 124.0, 113.3, 74.4, 42.0, 39.9, 26.3, 25.7, 23.9, 21.0, 17.6, 16.8. HRMS (CI) Calcd. for $C_{15}H_{27}O$

$(M+H)^+$: 223.2062, Found: 223.2057. FTIR (neat): 3415, 2965, 2915, 1667, 1638, 1445, 1414, 1377, 1360, 1266, 1182, 1099, 1009, 990, 909, 817, 741, 691 cm^{-1}. HPLC: Enantiomeric excess was determined by HPLC analysis of the 3,5-nitrobenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 99.5:0.5, 0.5 mL/min, 254 nm), t_{major} = 9.7 min, t_{minor} = 12.0 min; ee = 93% (aldehyde), 87% (alcohol).

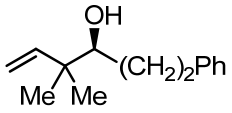
^1H NMR



^{13}C NMR



(*S*)-4,4-Dimethyl-1-phenylhex-5-en-3-ol

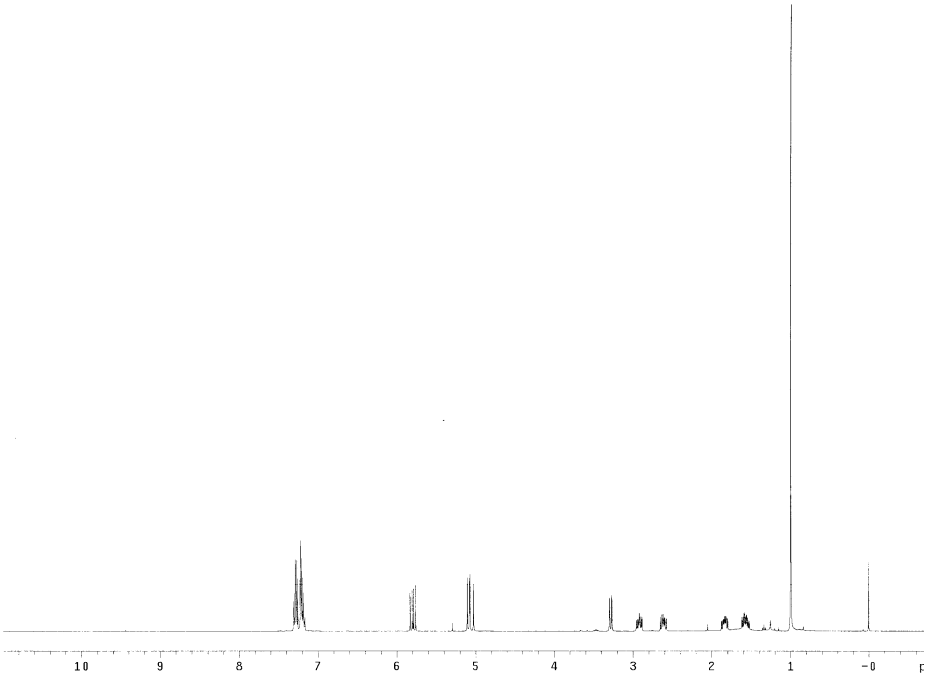


3.16f

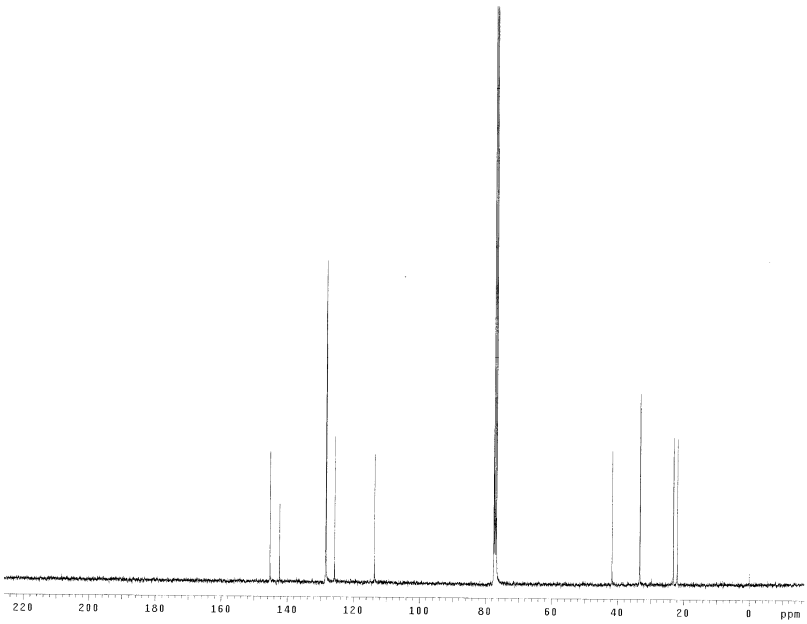
TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.17 (m, 5H), 5.79 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.09 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.05 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.28 (dd, *J* = 10.8, 1.6 Hz, 1H), 2.96-2.89 (m, 1H), 2.65-2.58 (m, 1H), 1.89-1.79 (m, 1H), 1.62-1.52 (m, 1H), 1.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 142.4, 128.5, 128.4, 125.8, 113.6, 77.5, 41.7, 33.3, 33.2, 23.1, 21.9. HPLC:

(Chiralcel OJ-H column, hexanes:*i*-PrOH = 97:3, 0.5 mL/min, 254 nm), t_{minor} = 11.6 min, t_{major} = 12.6 min; ee = 87% (aldehyde), 91% (alcohol).

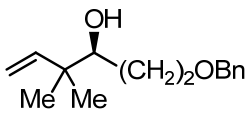
^{1}H NMR



^{13}C NMR



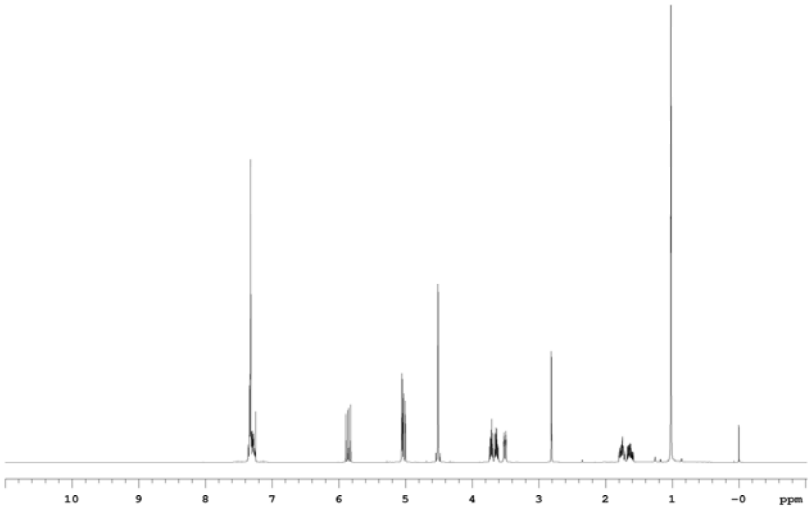
(*S*)-1-(Benzyloxy)-4,4-dimethylhex-5-en-3-ol



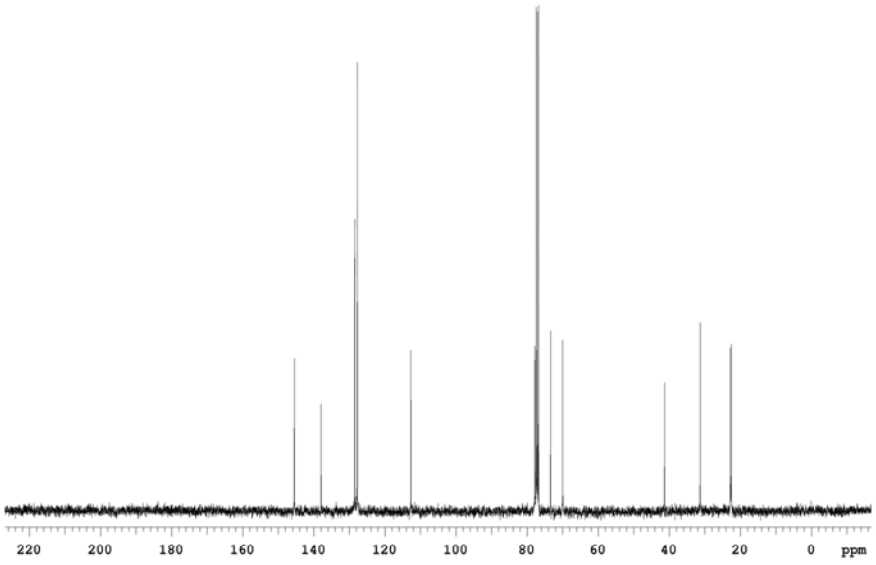
3.16g

TLC (SiO_2): R_f = 0.35 (ethyl acetate:hexanes, 1:7). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 5.86 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.04 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.02 (dd, *J* = 17.6, 1.6 Hz, 1H), 4.51 (d, *J* = 1.2 Hz, 2H), 3.74-3.49 (m, 2H), 3.51 (dt, *J* = 10.4, 2.4 Hz, 1H), 2.81(d, *J* = 2.8 Hz, 1H), 1.80-1.73 (m, 1H), 1.68- 1.58 (m, 1H), 1.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 137.9, 128.4, 127.7, 112.6, 77.7, 73.3, 69.9, 41.2, 31.2, 22.7, 22.5. HRMS (CI) Calcd. for $C_{15}H_{23}O_2(M+H)^+$: 235.1698, Found: 235.1696. FTIR (neat): 3480, 2962, 2864, 1638, 1496, 1454, 1415, 1362, 1309, 1205, 1078, 1028, 1005, 970, 911, 735, 696 cm^{-1}. HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm), t_{minor} = 11.4 min , t_{major} = 12.5 min; ee = 89% (aldehyde), 88% (alcohol)..

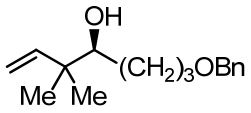
^{1}H NMR



^{13}C NMR



(*S*)-7-(Benzyloxy)-3,3-dimethylhept-1-en-4-ol

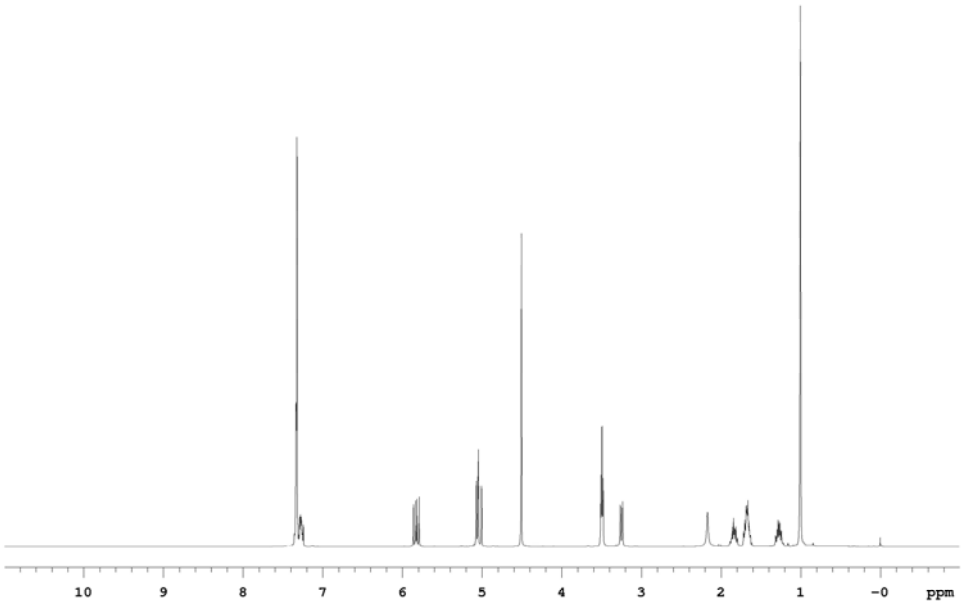


3.16h

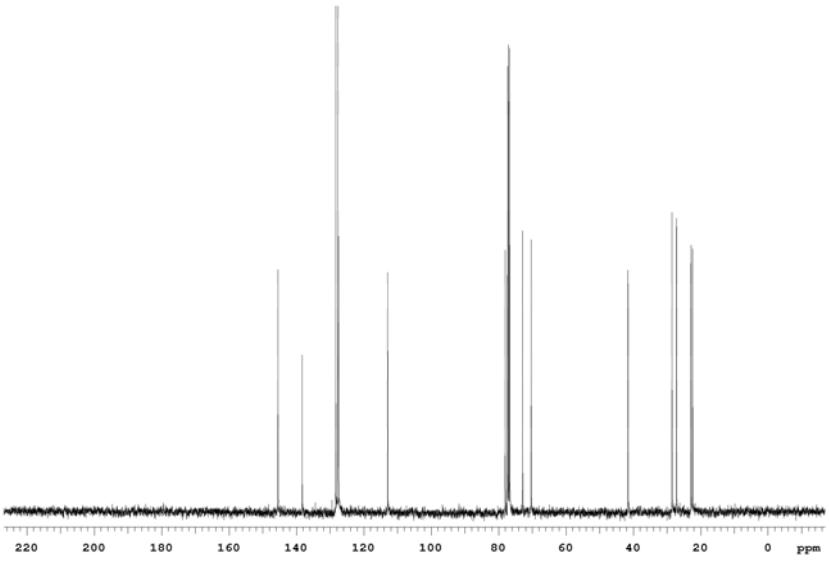
TLC (SiO_2): R_f = 0.35 (ethyl acetate:hexanes, 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.24 (m, 5H), 5.82 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.06 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.03 (dd, *J* = 17.6, 1.2 Hz, 1H), 4.51 (s, 1H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.25 (dd, *J* = 10.8, 1.2 Hz, 1H), 2.17 (br, 1H), 1.86-1.81 (m, 1H), 1.72- 1.63 (m, 2H), 1.32-1.24 (m, 1H), 1.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 138.3, 128.3, 127.6, 127.5, 112.9, 78.0, 72.8, 70.3, 41.5, 28.5, 27.2, 22.8, 22.4. HRMS (CI) Calcd. for $C_{16}H_{25}O_2(M+H)^+$: 249.1855, Found: 249.1857. FTIR (neat): 3478, 2959, 2862, 1637, 1496, 1454, 1414, 1361, 1274,

1204, 1091, 1028, 1005, 972, 910, 734, 696 cm^{-1}. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 97:3, 0.7 mL/min, 210 nm), t_{minor} = 11.6 min , t_{major} = 12.3 min; ee = 93% (aldehyde), 91% (alcohol).

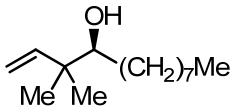
^{1}H NMR



^{13}C NMR



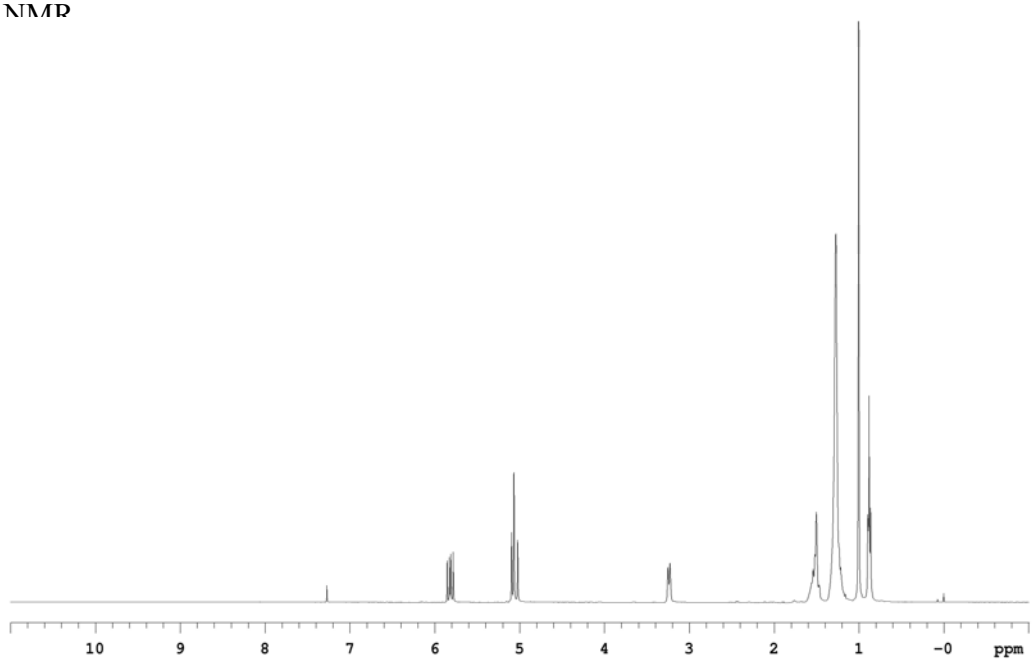
(*S*)-3,3-Dimethyldodec-1-en-4-ol



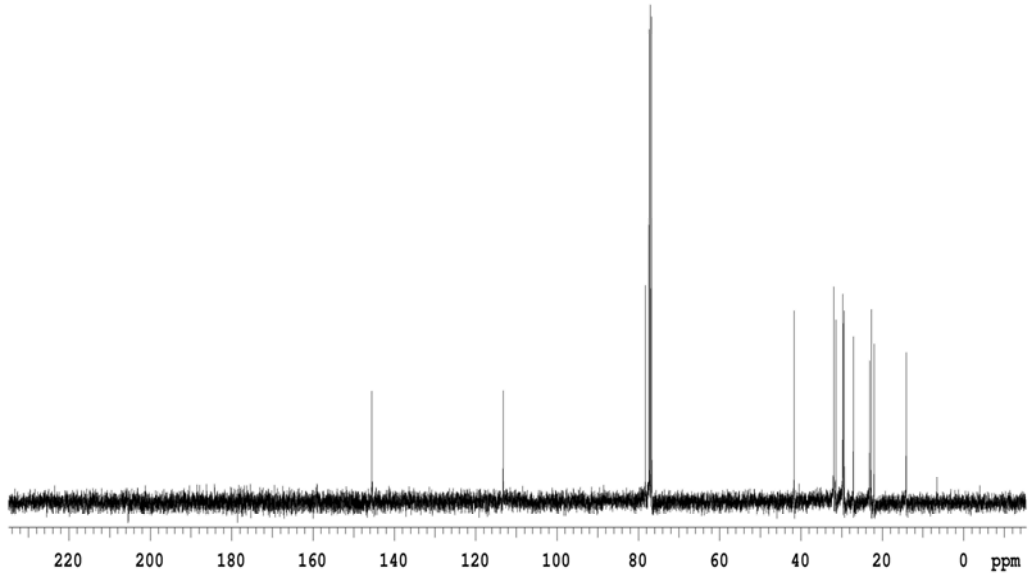
3.16i

TLC (SiO_2): R_f = 0.39 (ethyl acetate:hexanes, 1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 3.24 (d, *J* = 9.2 Hz, 1H), 1.56-1.46 (m, 2H), 1.34-1.22 (m,12H), 1.00 (s, 6H), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 113.2, 78.2, 41.6, 31.9, 31.4, 29.7, 29.6, 29.3, 27.1, 23.1, 22.7, 22.0, 14.1. HPLC: Enantiomeric excess was determined by HPLC analysis of the 3,5-nitrobenzoate derivative of the product (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 230 nm), t_{major} = 16.7 min, t_{minor} = 19.1 min; ee = 92% (aldehyde), 90% (alcohol).

^{1}H NMR



^{13}C NMR

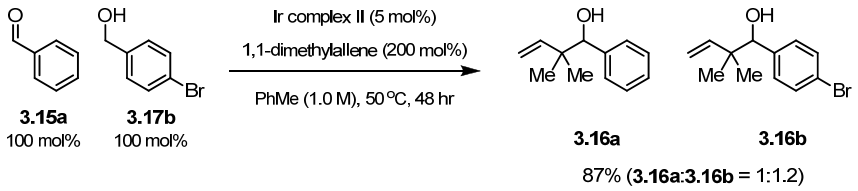


Procedure for the Preparation of Ir-Complex II

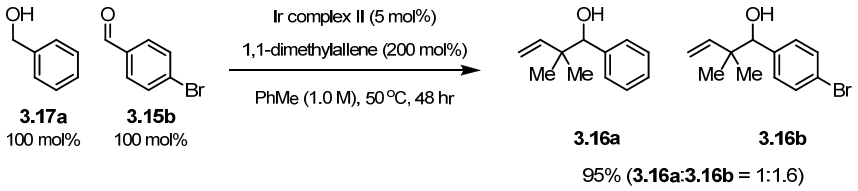
To a mixture of $[Ir(cod)Cl]_2$ (100 mg, 0.15 mmol, 100 mol%), BIPHEP (157 mg, 0.3 mmol, 200 mol%), Cs_2CO_3 (195 mg, 0.6 mmol, 400 mol%) and *m*-nitrobenzoic acid (100 mg, 0.6 mmol, 400 mol%) in a sealed tube under N_2 atmosphere was added THF (3 mL, 0.05 M). The reaction mixture was heated at 80 ^oC for 30 min and was then allowed to cool to the ambient temperature. Allyl acetate (75 mg, 0.75 mmol, 500 mol%) was added and the reaction mixture was allowed to stir for an additional 90 min at 80 ºC, at which point the reaction mixture was allowed to cool to the ambient temperature. The reaction mixture was filtered and washed with THF (15 mL) until all yellow residue was dissolved. The filtrate was concentrated *in vacuo* and hexanes (50 mL) was added. A

yellow precipitate formed, which was collected by filtration and dried under vacuum (213 mg, 0.231 mmol, 77% yield).

Competition Experiments



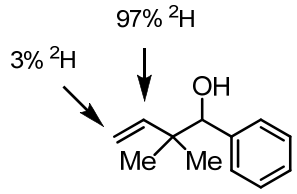
An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with **Ir-complex II** (23 mg, 0.025 mmol, 5 mol%) and toluene (1.0 M, 0.5 mL). Benzaldehyde **3.15a** (53 mg, 0.5 mmol, 100 mol%), 1,1-dimethylallene (68 mg, 1.0 mmol, 200 mol%) and 4-bromobenzyl alcohol **3.17b** (94 mg, 0.5 mmol, 100 mol%) were added and the reaction mixture was allowed to stir at 50 ^{o}C for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:hexanes, 1:50) provided a 1:1.2 mixture of **3.16a** and **3.16b** (95 mg, *ca.* 87%) as a colorless oil. (*N.B.* yield is based upon 100 mol% of alcohol as the limiting reagent and is calculated based upon product stoichiometry).



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with **Ir-complex II** (23 mg, 0.025 mmol, 5 mol%) and toluene (1.0 M, 0.5 mL). 4-Bromobenzaldehyde **3.15b** (93 mg, 0.5 mmol, 100 mol%), 1,1-dimethylallene (68 mg, 1.0 mmol, 200 mol%) and benzyl alcohol **3.17a** (54 mg, 0.5 mmol, 100 mol%) were added and the action mixture was allowed to stir at 50 ^{o}C for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:hexanes, 1:50) provided a 1:1.6 mixture of **3.16a** and **3.16b** (107 mg, *ca.* 95%) as a colorless oil. (*N.B.* yield is based upon 100 mol% of alcohol as the limiting reagent and is calculated based upon product stoichiometry).

Isotopic Labeling Experiments

3-*Deuterio*-2,2-dimethyl-1-phenylbut-3-en-1-ol



***deuterio*-3.16a**

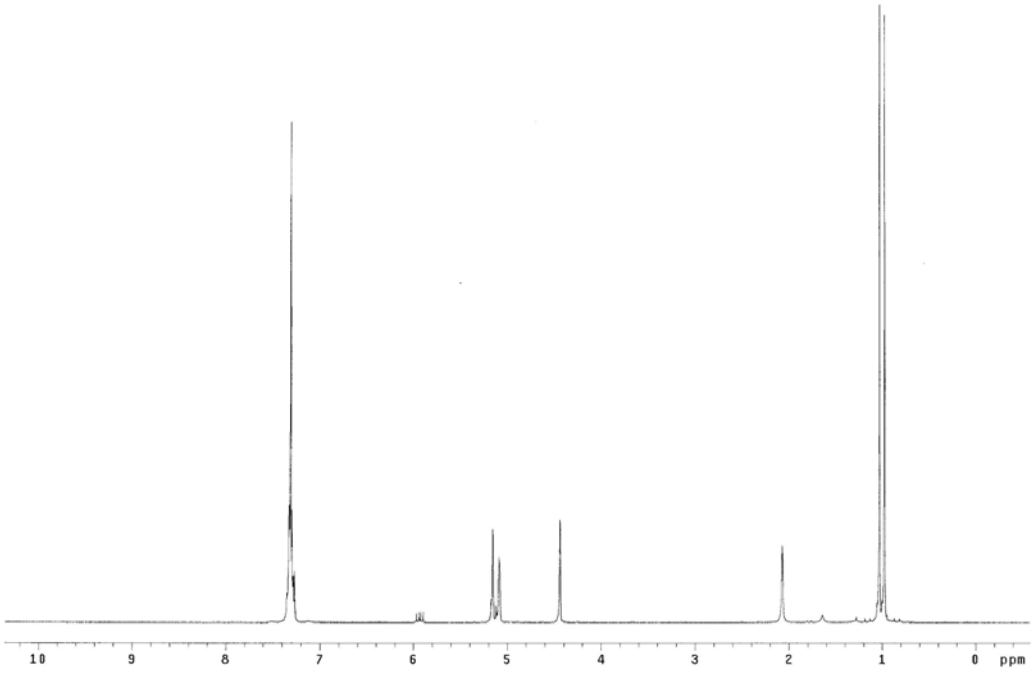
An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with **Ir-complex II** (23 mg, 0.025 mmol, 5 mol%) and toluene (1.0 M, 0.5 mL). Benzaldehyde **3.15a** (53 mg, 0.5 mmol, 100 mol%), 1,1-dimethylallene (68 mg, 1.0 mmol, 200 mol%) and d_8-isopropanol (68 mg, 1.0 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 50 ^{o}C for 48 hr, at which point the reaction

mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:hexanes, 1:50) provided ***deuterio*-3.16a** (65 mg, 0.365 mmol) as a colorless oil in 73% yield.

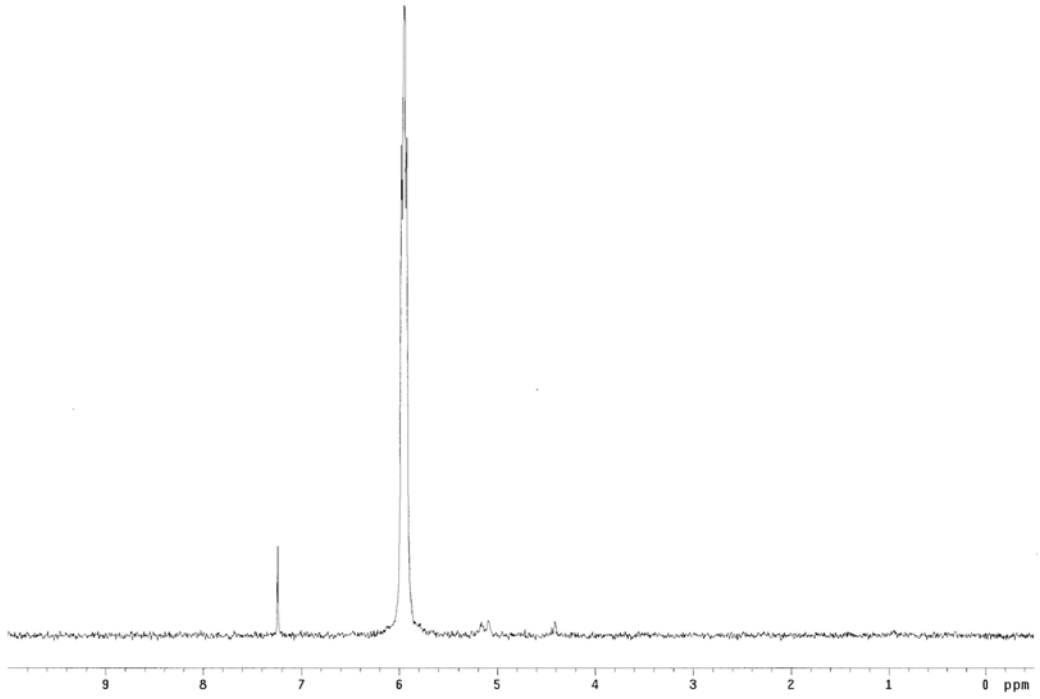
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 5H), 5.90 (dd, J = 17.6, 10.8 Hz, 0.18H), 5.18-5.09(m, 1.96H), 4.44 (s, 1H), 2.10 (s, 1H), 1.00 (s, 3H), 0.95 (s, 3H). ^{2}H NMR (77 MHz, $CHCl_3$): δ 5.95 (s, 0.97^{2}H), 5.18-5.07 (m, 0.03^{2}H)*.

*(this signal corresponds to 3% total ^{2}H incorporation in the terminal vinylic protons)

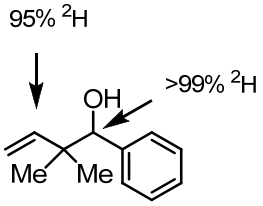
^{1}H NMR



^{2}H NMR



1,3-*Deuterio*-2,2-dimethyl-1-phenylbut-3-en-1-ol



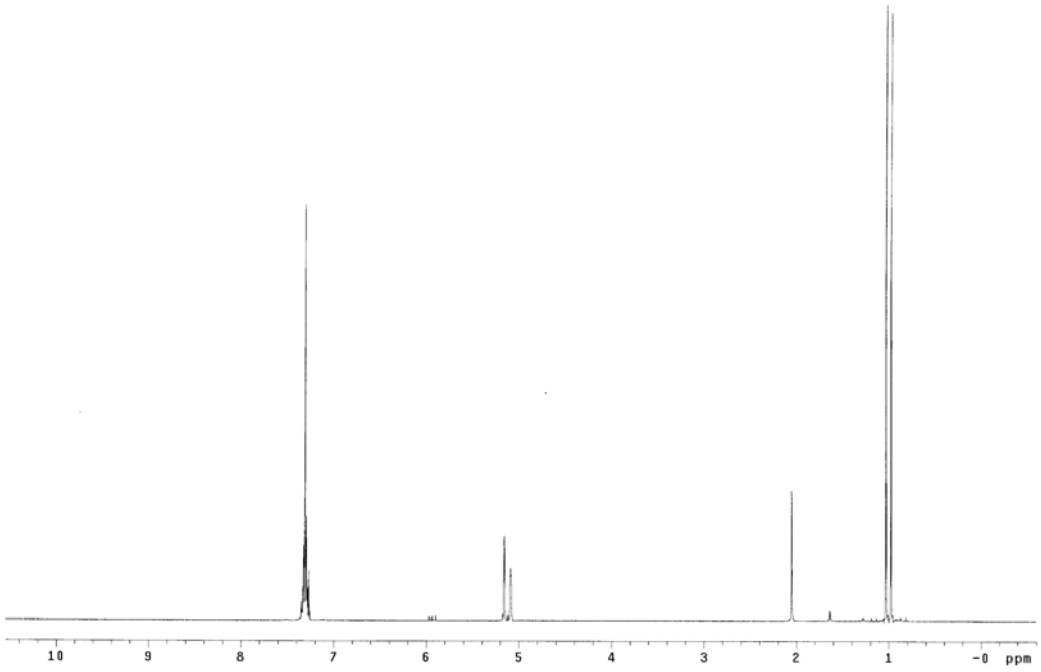
***deuterio*-3.16a'**

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with **Ir-complex II** (23 mg, 0.025 mmol, 5 mol%) and toluene (1.0 M, 0.5 mL). d_2-Benzyl alcohol (56 mg, 0.5 mmol, 100 mol%), 1,1-dimethylallene (68 mg, 1.0 mmol, 200 mol%) and propionaldehyde (1.5 mg, 0.025 mmol, 5 mol%) were added and the reaction

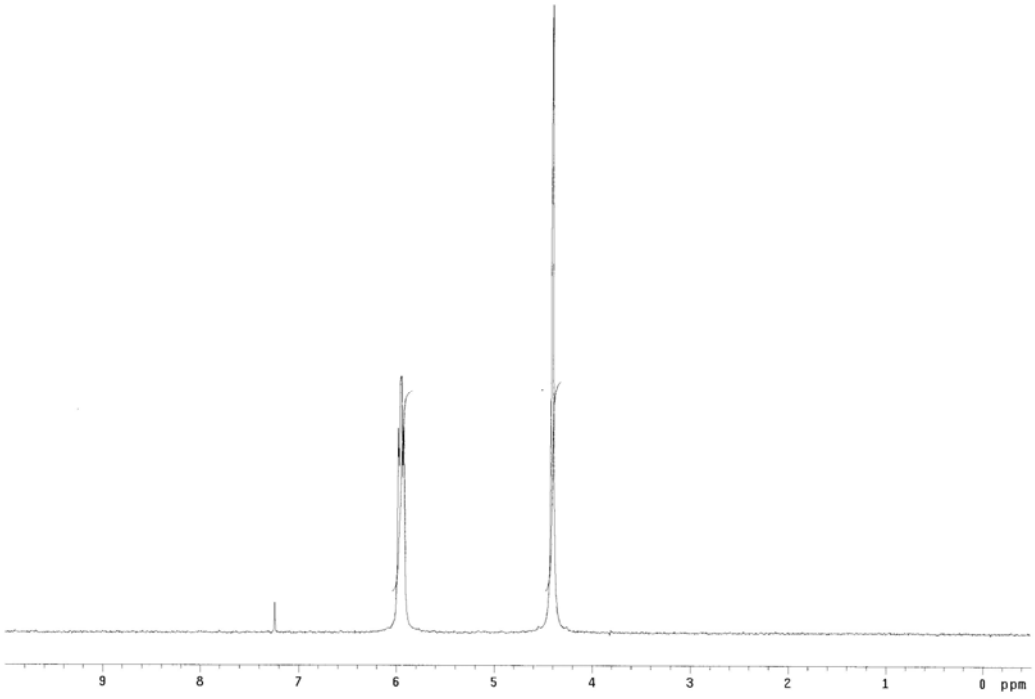
mixture was allowed to stir at 50 °C for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50) provided ***deuterio*-3.16a'** (70 mg, 0.392 mmol) as a colorless oil in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 5H), 5.90 (dd, *J* = 17.6, 10.8 Hz, 0.09H), 5.12 (d, *J* = 10.8 Hz, 1H), 5.06 (d, *J* = 17.6 Hz, 1H), 4.39 (s, 1H), 2.10 (s, 1H), 1.00 (s, 3H), 0.95 (s, 3H). ^{2}H NMR (77 MHz, $CHCl_3$): δ 5.95 (m, 0.95^{2}H), 4.40 (s, 1.0^{2}H).

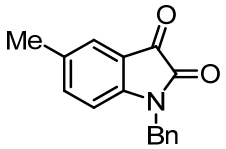
^{1}H NMR



^{2}H NMR



1-benzyl-5-methylindoline-2,3-dione



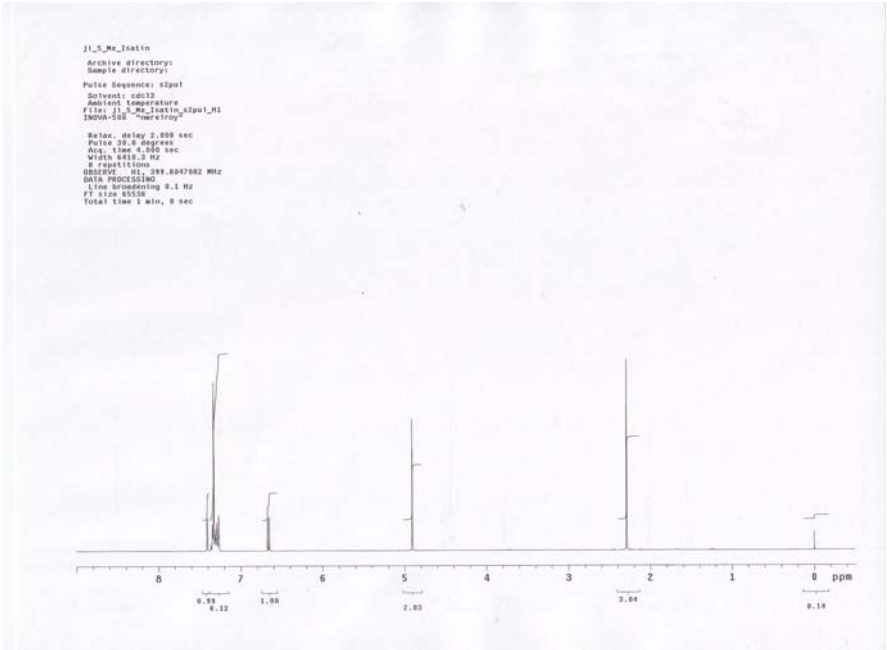
3.18c

5-Methyl isatin (1.50 g, 9.3 mmol, 100 mol%) was dissolved in *N*,*N*-dimethylformamide (18 mL), and then the organic solution was cooled to 0 ^{o}C. Sodium hydride (448.3 mg, 11.2 mmol, 60% dispersion in oil, 120 mol%) was added in one portion, and the reaction mixture was stirred at 0 ^{o}C for 20 min. Benzyl bromide (1.35 mL, 11.4 mmol, 120 mol%) was added dropwise at 0 ^{o}C. The reaction mixture was

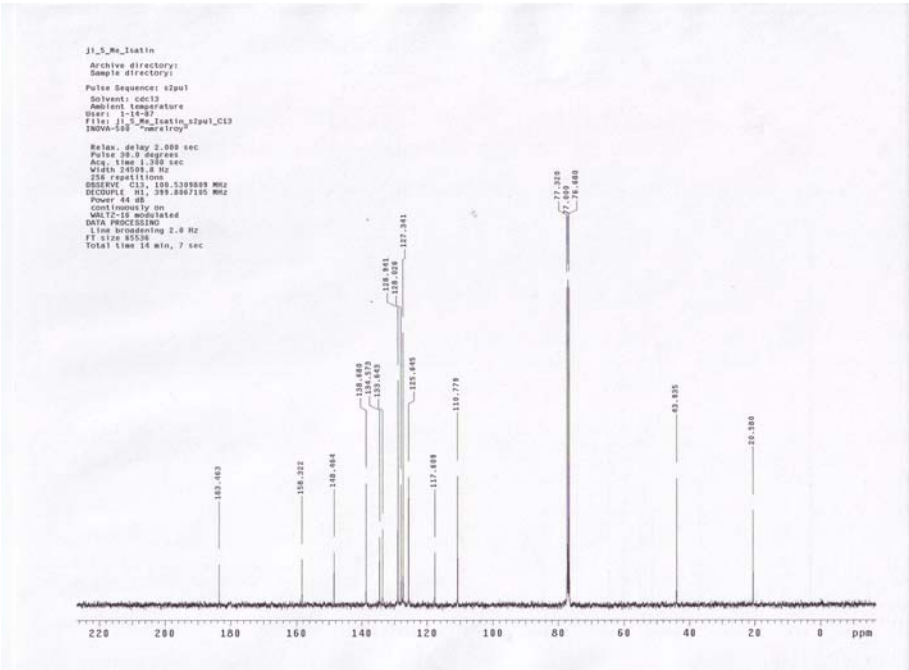
stirred at 0 ^{o}C for 30 min and allowed to stir overnight at the ambient temperature. Water was added to the reaction mixture, and a precipitate formed. The precipitate was filted and washed with water. This solid was recrystallized from ethanol, filtered and dried under reduced pressure to afford 1-benzyl-5-methylindoline-2,3-dione **3.18c** (1.84 g, 7.33 mmol, 77%).

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.26 (m, 7H), 6.66 (d, *J* = 8.2 Hz, 1H), 4.91 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.5, 158.3, 148.5, 138.7, 134.6, 133.6, 128.9, 128.0, 127.3, 125.6, 117.6, 110.8, 43.9, 20.6. FTIR (neat): υ 1726, 1618, 1598, 1488, 1450, 1367, 1350, 1338, 1314, 1227, 1203, 1173, 1126, 1081, 1024, 839, 819, 809, 775, 763, 719, 711, 967 cm^{-1}. HRMS (CI) Calcd. for $C_{16}H_{14}NO_2$ $(M+H)^+$: 252.1025, Found: 252.1026. mp (Ethanol) 146-147 ^{o}C, Red solid.

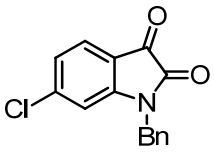
^{1}H NMR



^{13}C NMR



1-benzyl-6-chloroindoline-2,3-dione



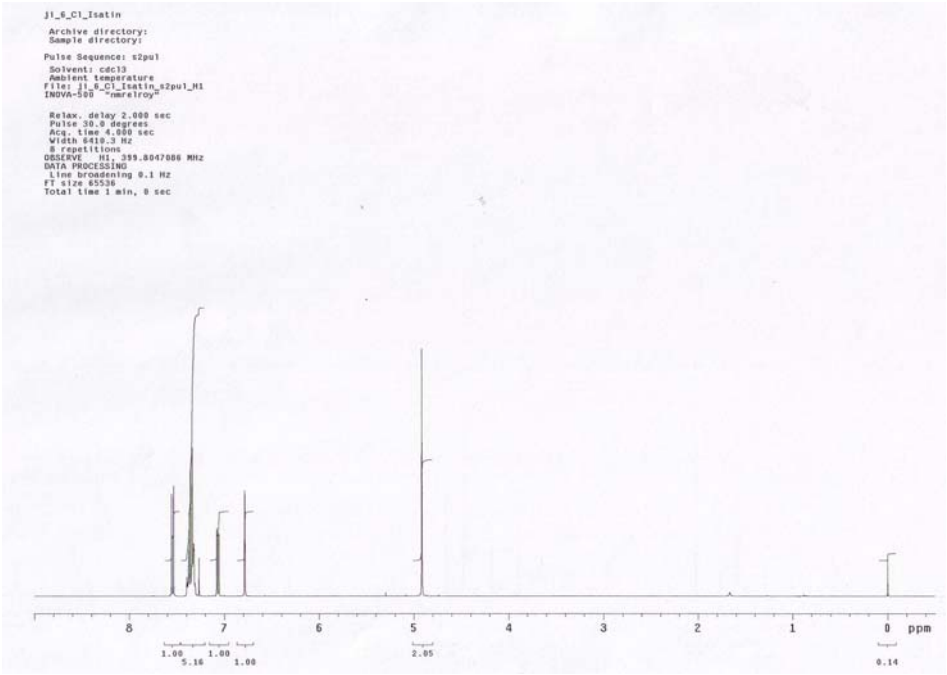
3.18e

6-Chloro isatin (1.51 g, 8.3 mmol, 100 mol%) was dissolved in *N*,*N*-dimethylformamide (18 mL), and then the organic solution was cooled to 0 ^{o}C. Sodium hydride (406.1 mg, 10.2 mmol, 60% dispersion in oil, 120 mol%) was added in one portion, and the reaction mixture was stirred at 0 ^{o}C for 20 min. Benzyl bromide (1.20 mL, 10.1 mmol, 120 mol%) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 min and allowed to stir overnight at the ambient temperature. Water

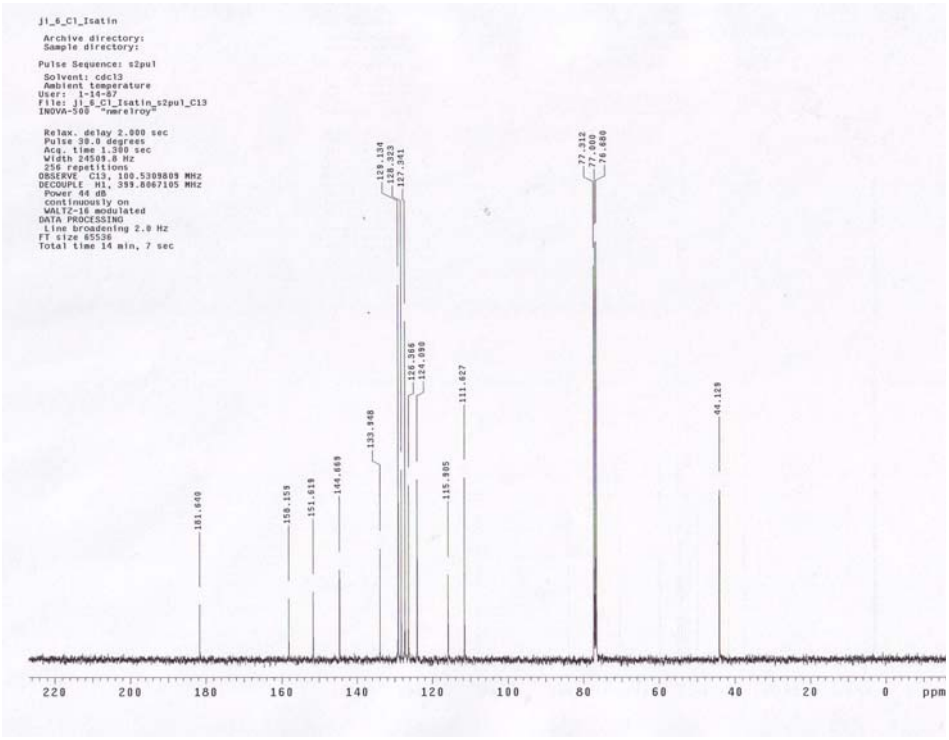
was added to the reaction mixture, and a precipitate formed. The precipitate was filted and washed with water. This solid was recrystallized from ethanol, filtered and dried under reduced pressure to afford 1-benzyl-6-chloroindoline-2,3-dione **3.18e** (1.68 g, 6.17 mmol, 74%).

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.40-7.30 (m, 5H), 7.07 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.79 (d, *J* = 1.7 Hz, 1H), 4.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.6, 158.2, 151.6, 144.7, 133.9, 129.1, 128.3, 127.3, 126.4, 124.1, 115.9, 111.6, 44.1. FTIR (neat): υ 1732, 1609, 1584, 1496, 1453, 1434, 1369, 1349, 1255, 1196, 1105, 1072, 1032, 878, 860, 837, 820, 753, 726, 716, 711, 698 cm^{-1}. HRMS (CI) Calcd. for $C_{15}H_{11}ClNO_2$ $(M+H)^+$: 272.0478, Found: 272.0477. mp (Ethanol) 173-174 ^{o}C, Orange solid

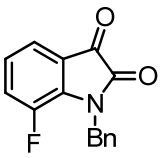
^{1}H NMR



^{13}C NMR



1-benzyl-7-fluoroindoline-2,3-dione



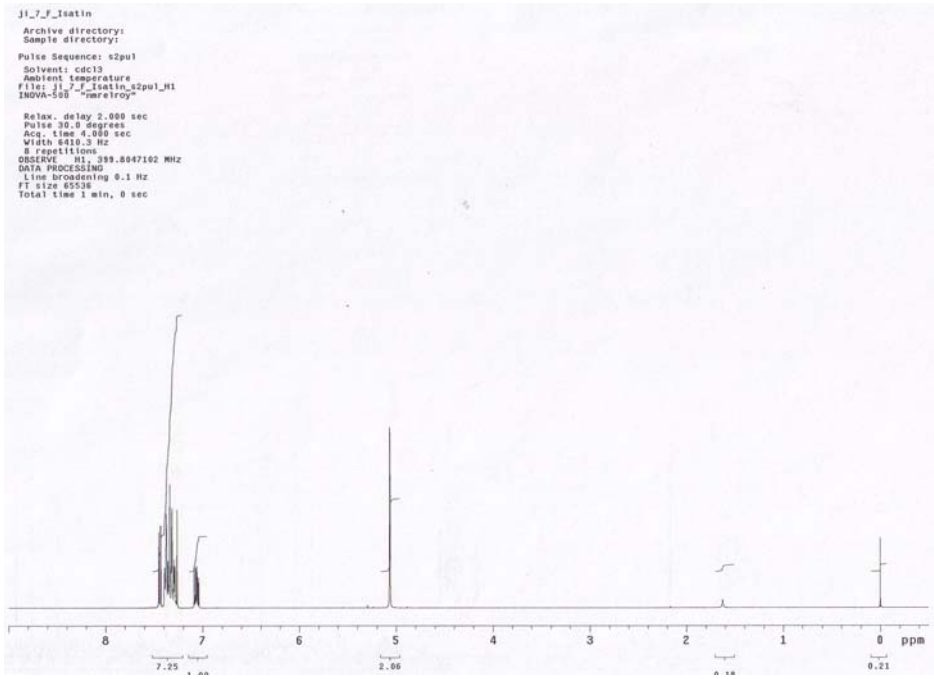
3.18g

7-Fluoro isatin (1.51 g, 9.1 mmol, 100 mol%) was dissolved in *N*,*N*-dimethylformamide (18 mL), and then the organic solution was cooled to 0 ^{o}C. Sodium hydride (439.0 mg, 11.0 mmol, 60% dispersion in oil, 120 mol%) was added in one portion, and the reaction mixture was stirred at 0 ^{o}C for 20 min. Benzyl bromide (1.30 mL, 11.0 mmol, 120 mol%) was added dropwise at 0 ^{o}C. The reaction mixture was

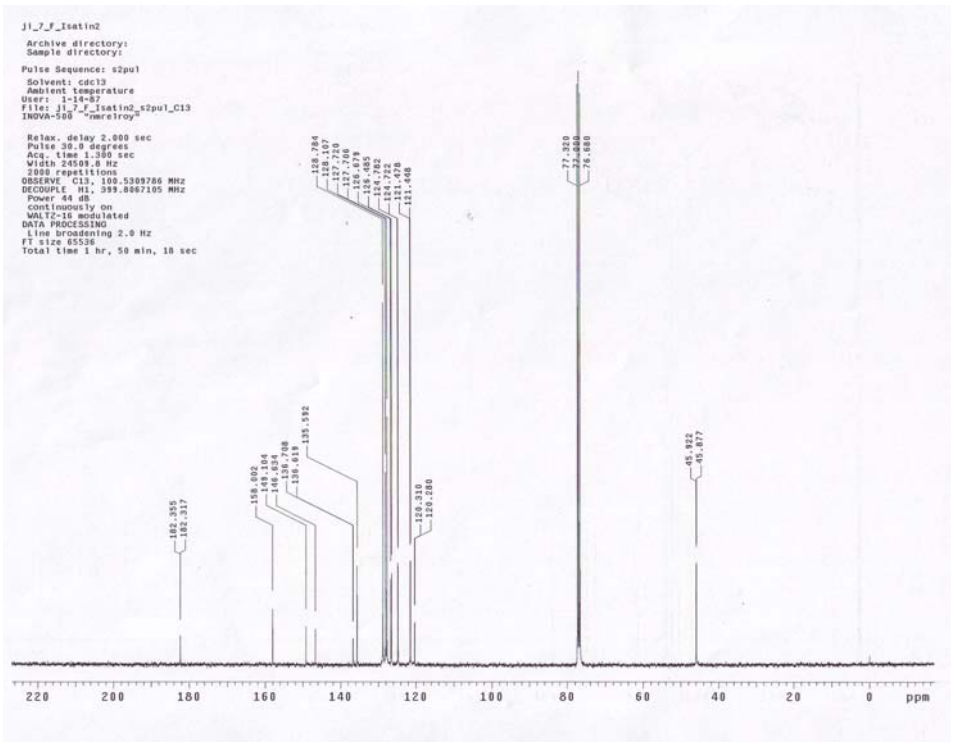
stirred at 0 ^{o}C for 30 min and allowed to stir overnight at the ambient temperature. Water was added to the reaction mixture, and a precipitate formed. The precipitate was filted and washed with water. This solid was recrystallized from ethanol, filtered and dried under reduced pressure to afford 1-benzyl-7-fluoroindoline-2,3-dione **3.18g** (1.79 g, 7.03 mmol, 77%).

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.39-7.26 (m, 6H), 7.09-7.04 (m, 1H), 5.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.3 (d, J_{C-F}= 3.8 Hz), 158.0, 147.9 (d, J_{C-F}= 248.3 Hz), 136.7 (d, J_{C-F}= 8.9 Hz), 135.6, 128.8, 128.1, 127.7 (d, J_{C-F}= 1.4 Hz), 126.6 (d, J_{C-F}= 19.5 Hz), 124.8 (d, J_{C-F}= 6.0 Hz), 121.5 (d, J_{C-F}= 3.0 Hz), 120.3 (d, J_{C-F}= 3.0 Hz), 45.9 (d, J_{C-F}= 4.5 Hz). FTIR (neat): υ 1748, 1731, 1623, 1487, 1455, 1369, 1339, 1320, 1244, 1205, 1171, 1149, 1114, 1063, 1035, 968, 924, 822, 778, 755, 710, 700, 689 cm^{-1}. HRMS (CI) Calcd. for $C_{15}H_{11}FNO_2$ (M+1): 256.0774, Found: 256.0775. mp (Ethanol) 155-156 ^{o}C, Orange solid

^{1}H NMR

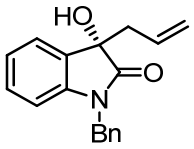


^{13}C NMR



Pocedure for Enantioselective Allylation of Isatins 1a-1f and Spectral Data for Adducts 3.19a-3.19f

(*S*)-3-allyl-1-benzyl-3-hydroxyindolin-2-one



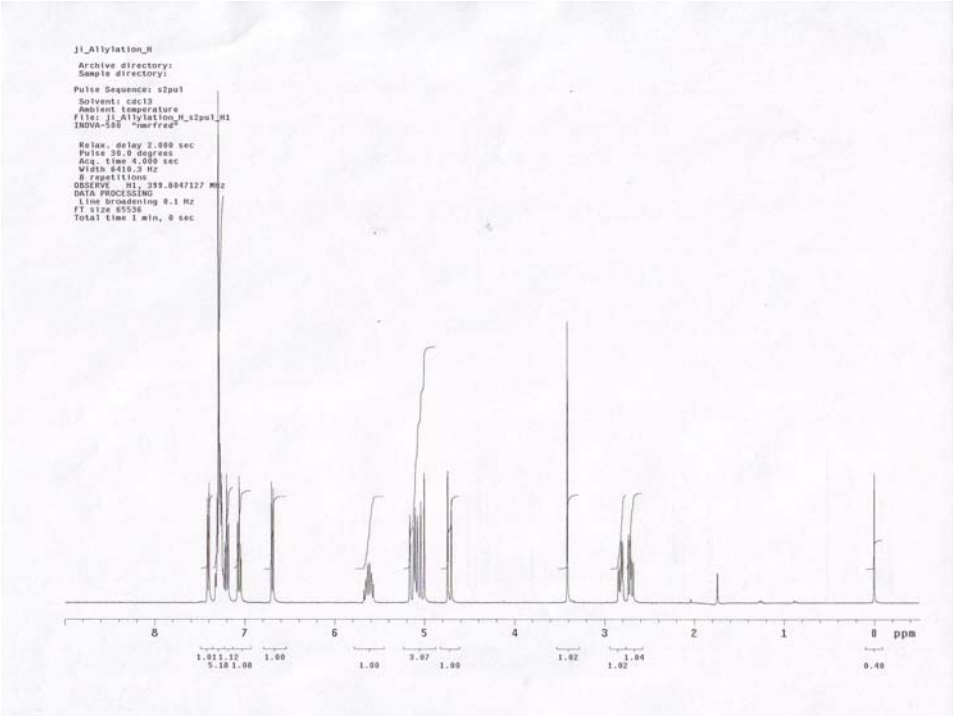
3.19a

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzylindoline-2,3-dione **3.18a** (46.9 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.040 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (45 μL, 0.414 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.19a** (40.1 mg, 0.144 mmol) as a white solid in 73% yield.

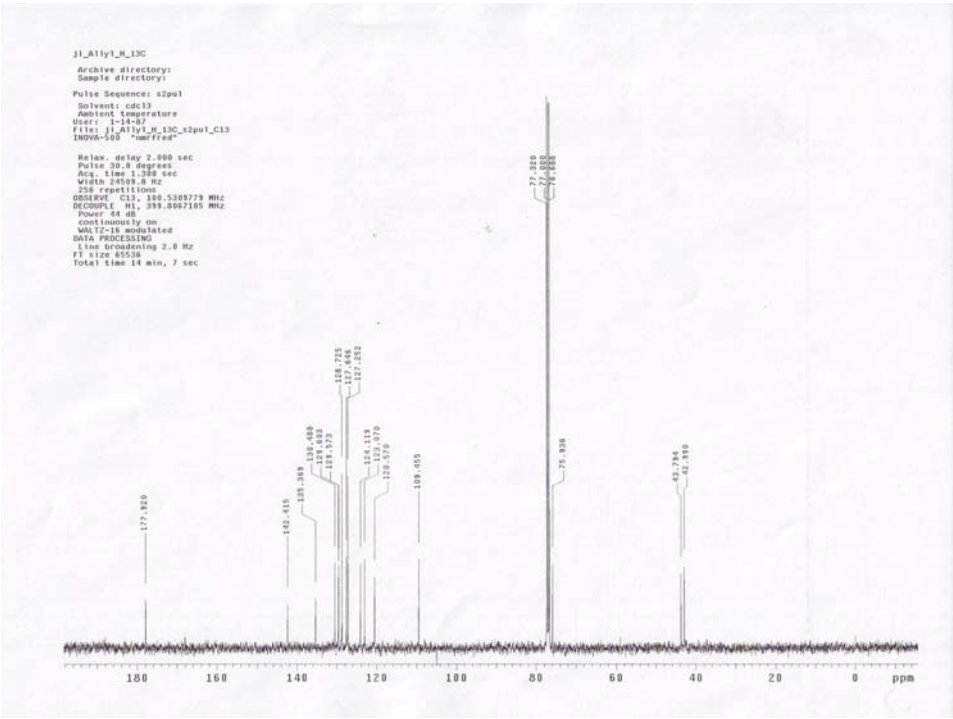
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.2 Hz, 1H), 7.32-7.18 (m, 6H), 7.08-7.04 (m, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.67-5.57 (m, 1H), 5.16-5.08 (m, 2H), 5.02 (d, *J* = 15.7 Hz, 1H), 4.72 (d, *J* = 15.7 Hz, 1H), 3.41 (brs, 1H), 2.85-2.80 (m, 1H), 2.74-2.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 142.4, 135.4, 130.5, 129.6, 129.6, 128.7, 127.6, 127.3, 124.1, 123.1, 120.6, 109.5,

75.9, 43.8, 43.0. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{minor} = 13.5 min, t_{major} = 24.9 min; ee = 91%., $[\alpha]_D^{26}$ –8.9 (c 1.01, $CHCl_3$) FTIR (neat): υ 3281, 1691, 1615, 1495, 1469, 1437, 1389, 1375, 1358, 1289, 1180, 1137, 1113, 1080, 990, 938, 919, 779, 757, 744, 697, 667 cm^{-1}. HRMS (CI) Calcd. for $C_{18}H_{17}NO_2$: 279.1259, Found: 279.1261. mp (DCM/Hexane) 152-154 ^oC, White solid

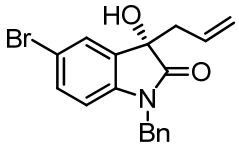
^1H NMR



^{13}C NMR



(*S*)-3-allyl-1-benzyl-5-bromo-3-hydroxyindolin-2-one



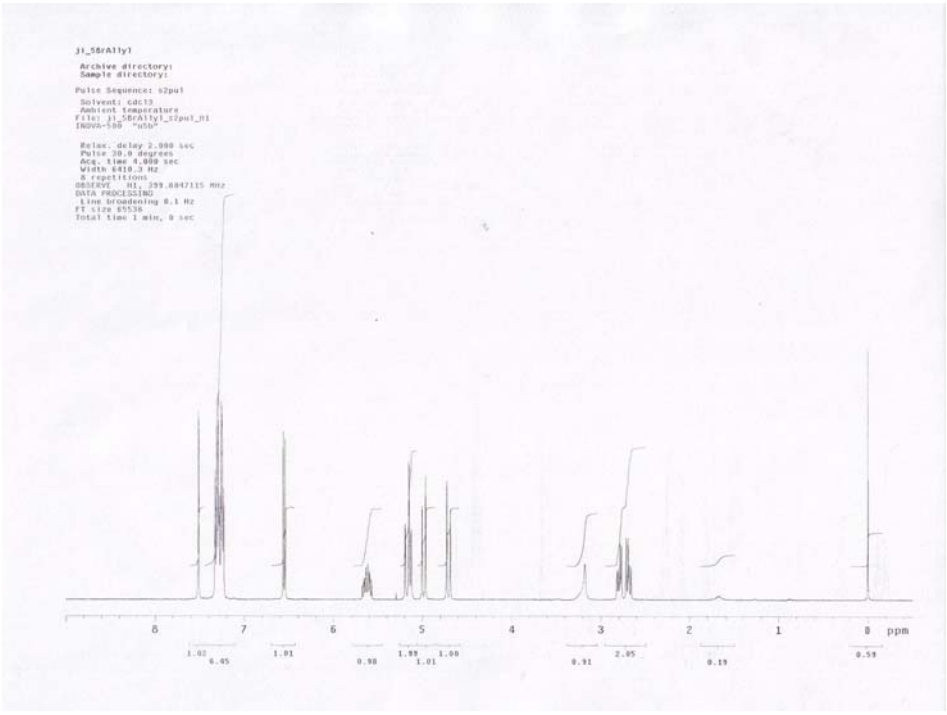
3.19b

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-5-bromoindoline-2,3-dione **3.18b** (62.6 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (6.5 mg, 0.02 mmol, 10 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient

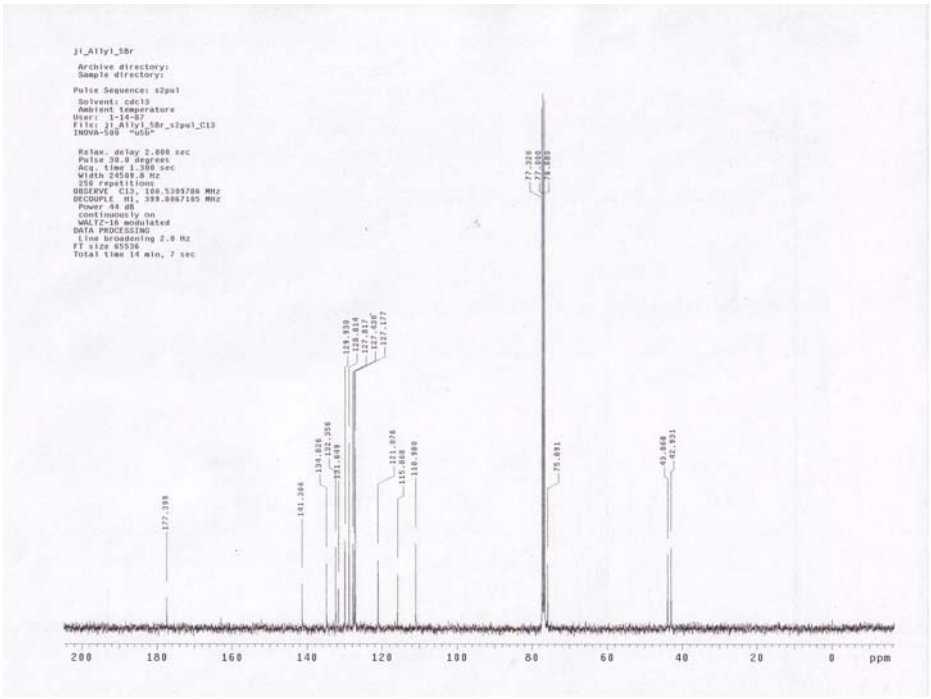
temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (45 μL, 0.414 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.19b** (57.3 mg, 0.160 mmol) as a white solid in 80% yield.

TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.33-7.23 (m, 6H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.68-5.57 (m, 1H), 5.20-5.13 (m, 2H), 4.98 (d, *J* = 15.8 Hz, 1H), 4.71 (d, *J* = 15.8 Hz, 1H), 3.18 (brs, 1H), 2.79 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.69 (dd, *J* = 13.3, 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 141.4, 134.8, 132.4, 131.6, 129.9, 128.8, 127.8, 127.4, 127.2, 121.1, 115.9, 111.0, 75.9, 43.9, 42.9. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{minor} = 13.0 min, t_{major} = 20.2 min; ee = 94%., $[\alpha]_D^{25}$ –6.0 (c 1.01, $CHCl_3$). FTIR (neat): υ 3349, 2917, 1693, 1606, 1496, 1479, 1456, 1428, 1362, 1343, 1174, 1070, 1025, 922, 817, 742, 698, 675, 655 cm^{-1}. HRMS (CI) Calcd. for $C_{18}H_{16}BrNO_2$: 357.0364, Found: 357.0366. mp (DCM/Hexane) 98-99 ^{o}C, White solid.

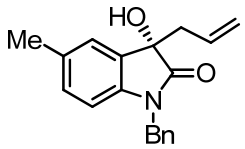
^{1}H NMR



^{13}C NMR



(*S*)-3-allyl-1-benzyl-3-hydroxy-5-methylindolin-2-one



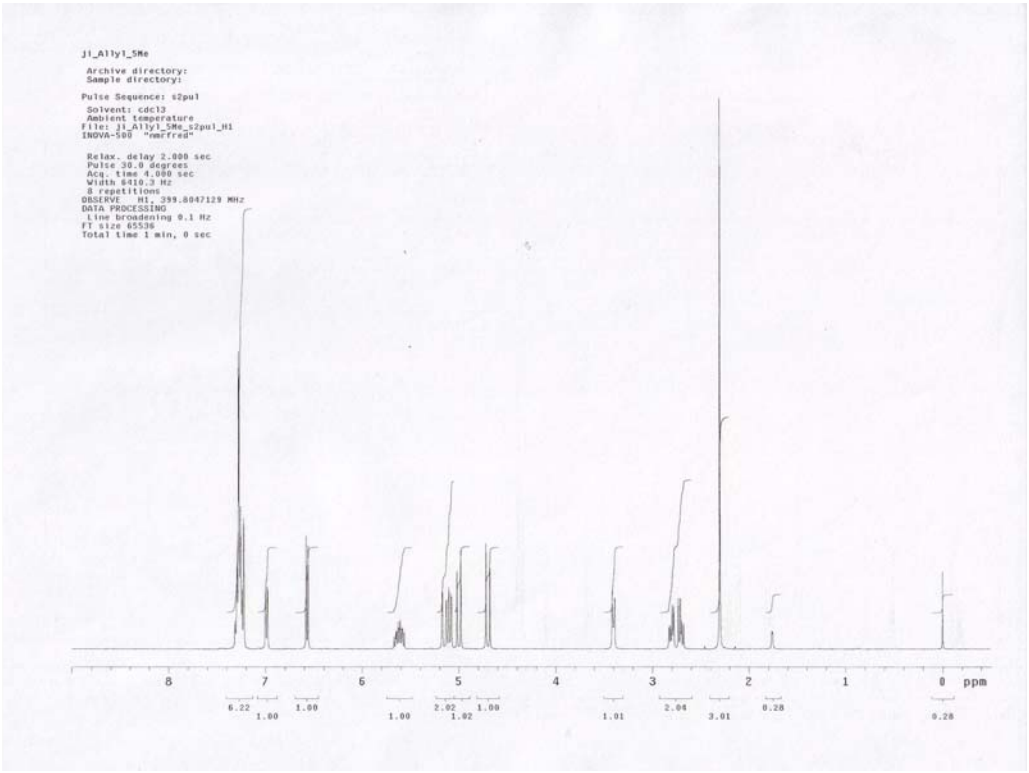
3.19c

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-5-methylindoline-2,3-dione **3.18c** (50.2 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.040 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (45 μL, 0.414 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.19c** (52.3 mg, 0.178 mmol) as a white solid in 89% yield.

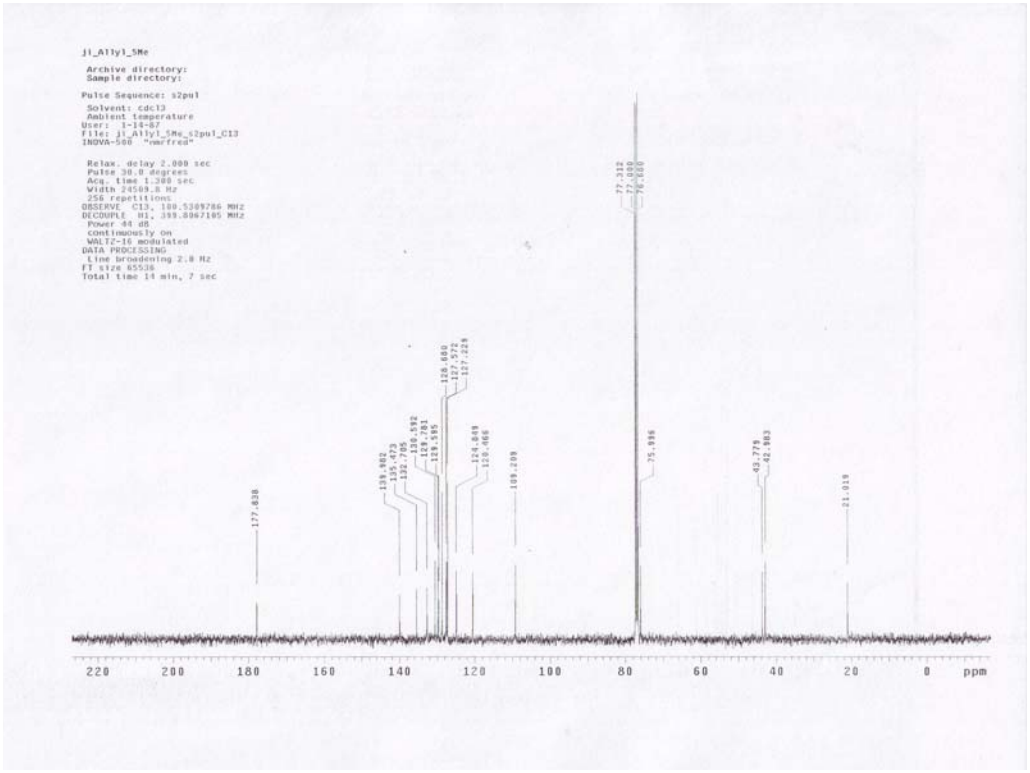
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.22 (m, 6H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.67-5.57 (m, 1H), 5.17-5.08 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 3.40 (brs, 1H), 2.81 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.71 (dd, *J* = 13.2, 8.6 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.8, 140.0, 135.5, 132.7, 130.6, 129.8, 129.6, 128.7, 127.6, 127.2, 124.8, 120.5, 109.2, 76.0, 43.8, 43.0, 21.0. HPLC: (Chiralpak AD-H column, hexanes:*i*-

PrOH = 90:10, 0.8 mL/min, 254 nm), t_{minor} = 13.8 min, t_{major} = 15.7 min; ee = 92%., $[\alpha]_D^{26}$ –6.0 (c 1.00, $CHCl_3$). FTIR (neat): υ 3265, 2922, 1692, 1625, 1604, 1495, 1435, 1399, 1374, 1349, 1282, 1243, 1193, 1155, 1130, 1093, 1079, 990, 928, 803, 781, 750, 733, 700, 655 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{19}NO_2$: 293.1416, Found: 293.1417. mp (DCM/Hexane) 156-157 ^oC, White solid.

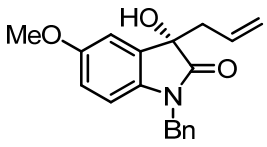
^1H NMR



^{13}C NMR



(*S*)-3-allyl-1-benzyl-3-hydroxy-5-methoxyindolin-2-one



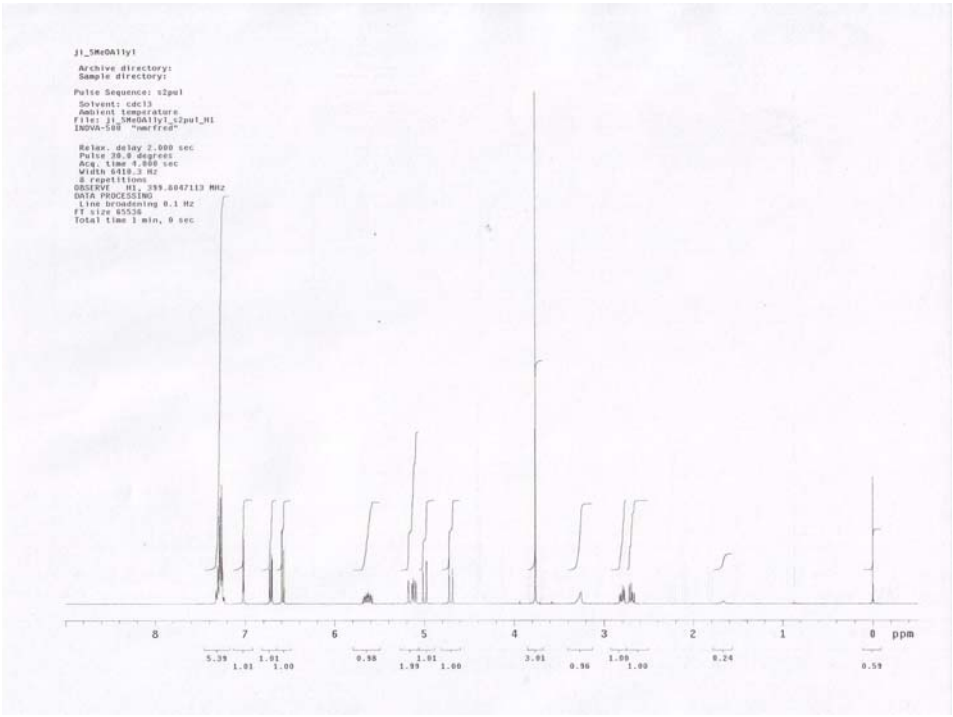
3.19d

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-5-methoxyindoline-2,3-dione **3.18d** (52.3 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.040 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient

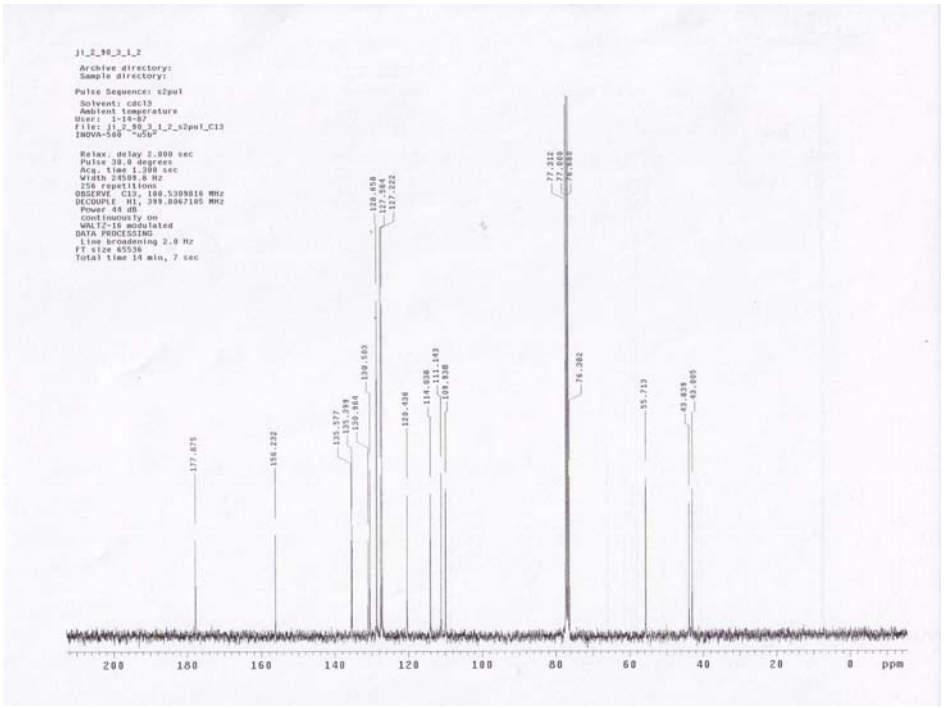
temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (45 μL, 0.414 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.19d** (55.4 mg, 0.179 mmol) as a white solid in 92% yield.

TLC (SiO_2): R_f = 0.3 (hexane:ethyl acetate, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 7.02 (d, *J* = 2.7 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 5.69-5.58 (m, 1H), 5.19-5.09 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 3.76 (s, 3H), 3.25 (brs, 1H), 2.80 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.69 (dd, *J* = 13.3, 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 156.2, 135.6, 135.4, 131.0, 130.5, 128.7, 127.6, 127.2, 120.4, 114.0, 111.1, 109.9, 76.4, 55.7, 43.8, 43.0. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{minor} = 16.4 min, t_{major} = 26.8 min; ee = 94%., $[\alpha]_D^{25}$ –13.1 (c 0.99, $CHCl_3$). FTIR (neat): υ 3265, 2926, 1689, 1610, 1498, 1473, 1435, 1402, 1379, 1352, 1299, 1277, 1257, 1198, 1184, 1168, 1134, 1119, 1089, 1080, 1043, 1020, 1003, 994, 971, 926, 889, 862, 810, 780, 763, 748, 731, 701, 661 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{19}NO_2$: 309.1365, Found: 309.1370. mp (DCM/Hexane) 156-157 ^{o}C, White solid.

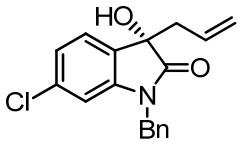
^{1}H NMR



^{13}C NMR



(*S*)-3-allyl-1-benzyl-6-chloro-3-hydroxyindolin-2-one



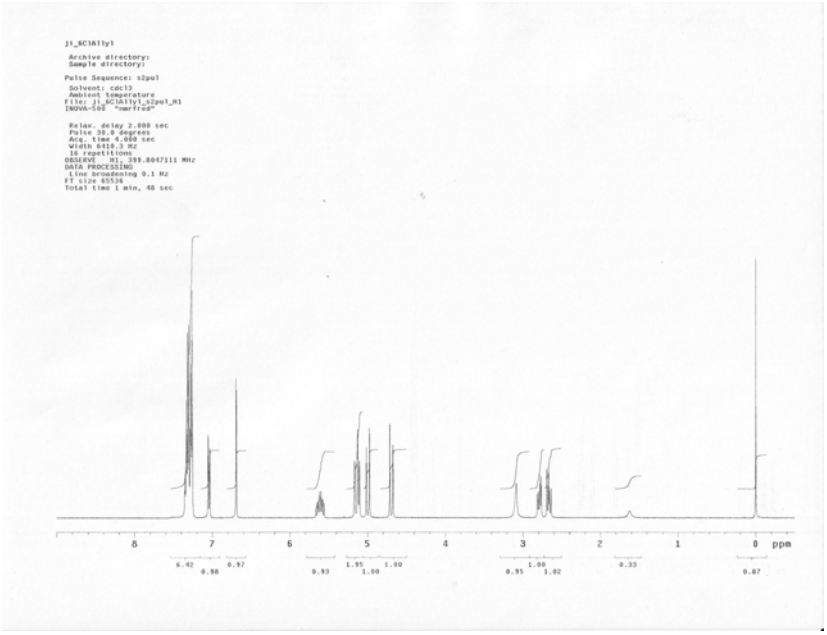
3.19e

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-6-chloroindoline-2,3-dione **3.18e** (53.5 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.040 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (45 μL, 0.414 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20) provided **3.19e** (45.3 mg, 0.144 mmol) as a white solid in 73% yield.

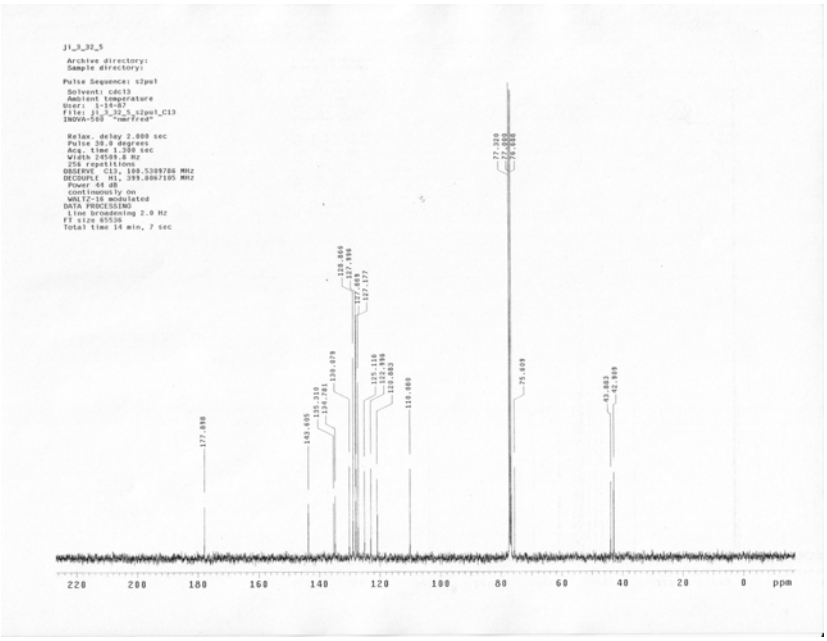
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 7.04 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.69 (d, *J* = 1.8 Hz, 1H), 5.66-5.56 (m, 1H), 5.17-5.10 (m, 2H), 4.99 (d, *J* = 15.8 Hz, 1H), 4.69 (d, *J* = 15.8 Hz, 1H), 3.08 (brs, 1H), 2.79 (dd, *J* = 13.2, 6.2 Hz, 1H), 2.66 (dd, *J* = 13.2, 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 143.6, 135.3, 134.8, 130.1, 128.9, 128.0, 127.9, 127.2, 125.1, 123.0, 120.9, 110.1, 75.6, 43.9, 42.9. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 35.9 min, t_{major} = 37.2 min; ee = 96%., $[\alpha]_D^{26}$ –23.0 (c 1.00,

$CHCl_3$). FTIR (neat): υ 3384, 3030, 1708, 1610, 1489, 1434, 1374, 1352, 1174, 1115, 1071, 1029, 991, 924, 841, 817, 753, 698 cm^{-1}. HRMS (CI) Calcd. for $C_{18}H_{17}ClNO_2$ (M+1): 314.0948, Found: 314.0945. mp (DCM/Hexane) 163-164 ^oC, White solid

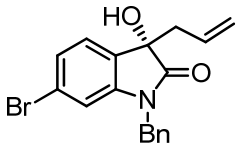
^1H NMR



^{13}C NMR



(*S*)-3-allyl-1-benzyl-6-bromo-3-hydroxyindolin-2-one



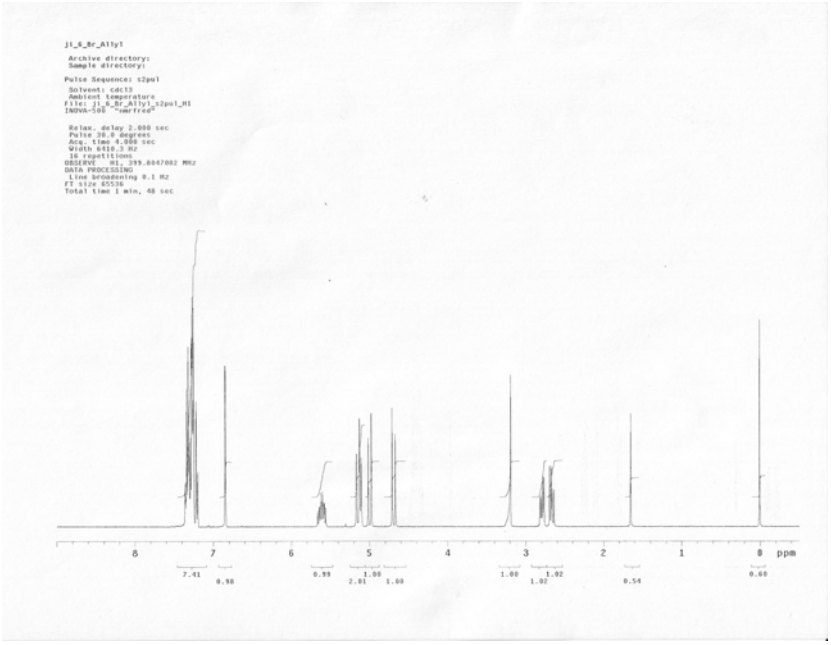
3.19f

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-6-bromoindoline-2,3-dione **3.18f** (63.1 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (6.5 mg, 0.02 mmol, 10 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (45 μL, 0.414 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20) provided **3.19f** (57.3 mg, 0.160 mmol) as a white solid in 80% yield.

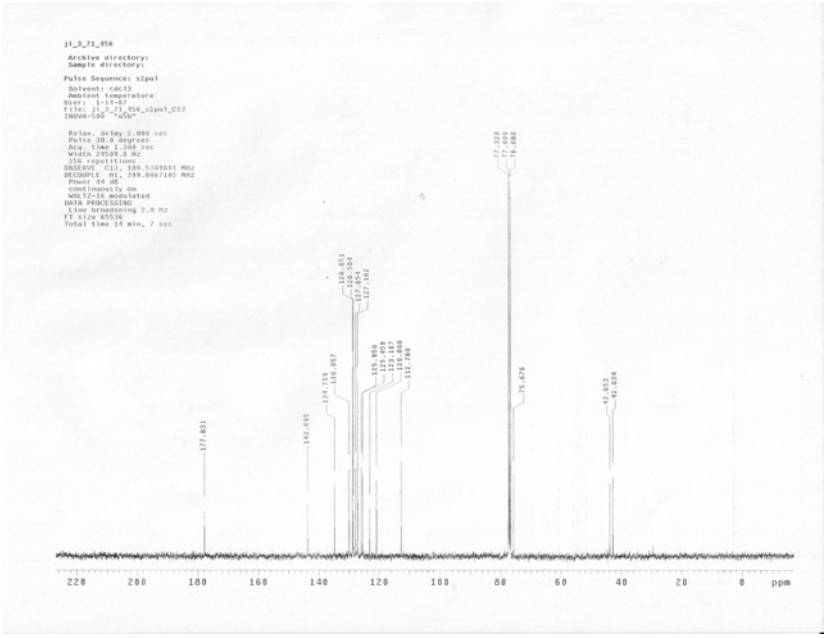
TLC (SiO_2): R_f = 0.2 (toluene:ethyl acetate, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.20 (m, 7H), 6.85 (d, *J* = 1.6 Hz, 1H), 5.66-5.56 (m, 1H), 5.17-5.10 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.69 (d, *J* = 15.7 Hz, 1H), 3.19 (brs, 1H), 2.79 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.67 (dd, *J* = 13.3, 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.8, 143.7, 134.8, 130.1, 128.9, 128.6, 127.9, 127.2, 126.0, 125.5, 123.2, 120.9, 112.8, 75.7, 43.9, 42.8. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 35.0 min, t_{major} = 39.4 min; ee = 94%., $[\alpha]_D^{25}$ –6.9 (c 1.01, $CHCl_3$). FTIR (neat): υ 3391,

3066, 2923, 1707, 1605, 1486, 1429, 1352, 1173, 1116, 1079, 1059, 990, 923, 835, 815, 738, 697 cm^{-1}. HRMS (CI) Calcd. for $C_{18}H_{17}BrNO_2$ (M+1): 358.0443, Found: 358.0438. mp (DCM/Hexane) 163-164 ^oC, White solid

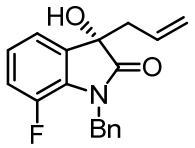
^1H NMR



^{13}C NMR



(*S*)-3-allyl-1-benzyl-7-fluoro-3-hydroxyindolin-2-one



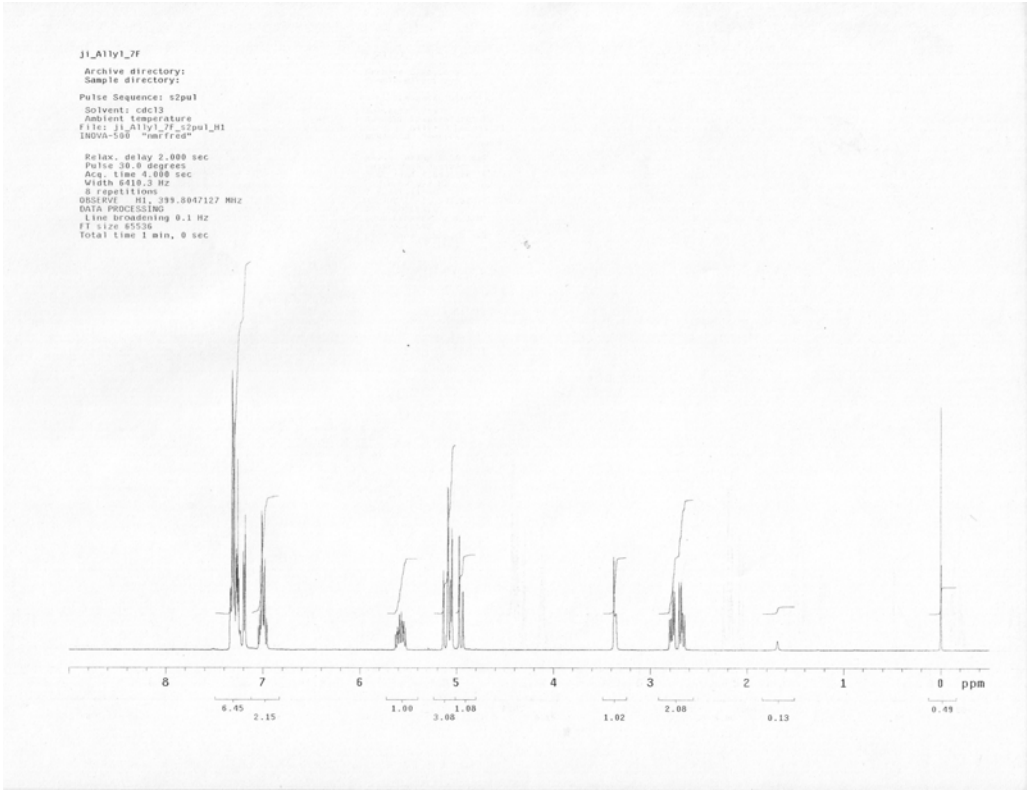
3.19g

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-7-fluoroindoline-2,3-dione **3.18g** (50.7 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.040 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and allyl acetate (86 μL, 0.8 mmol, 400 mol%) were added and the reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20) provided **3.19g** (38.5 mg, 0.130 mmol) as a white solid in 65% yield

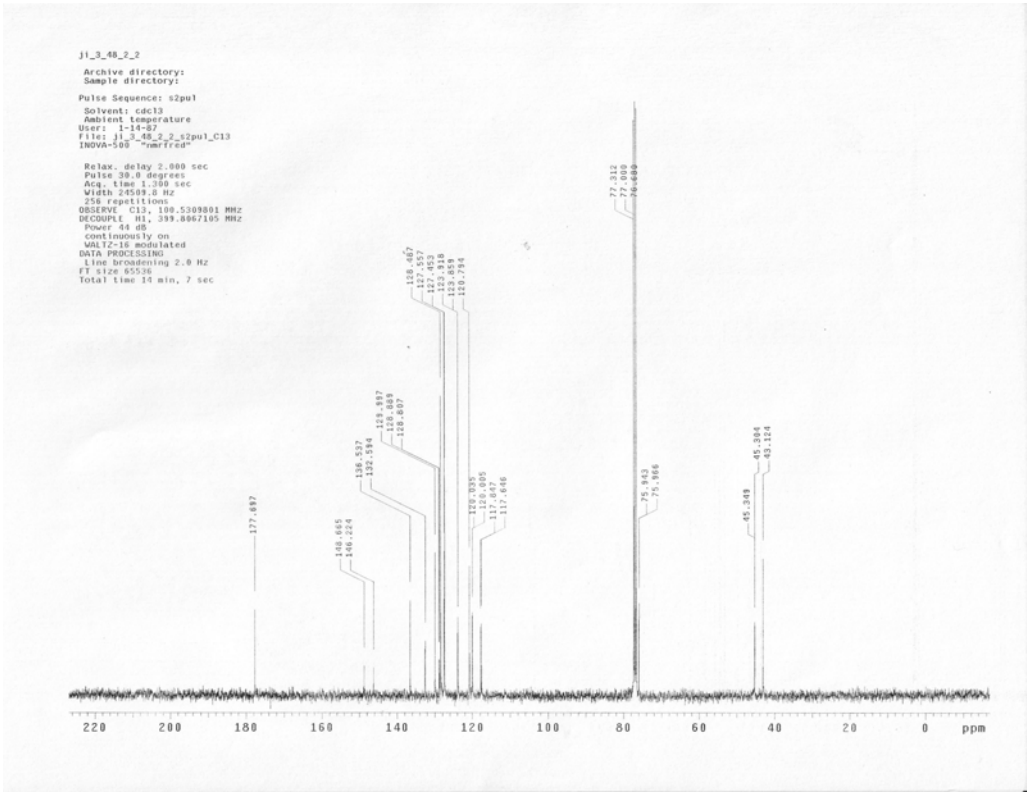
TLC (SiO_2): R_f = 0.2 (toluene:ethyl acetate, 10:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.16 (m, 6H), 7.04-6.96 (m, 2H), 5.63-5.53 (m, 1H), 5.14-5.05 (m, 3H), 4.95 (d, J = 15.5 Hz, 1H), 3.38 (brs, 1H), 2.78 (dd, J = 13.3, 6.3 Hz, 1H), 2.68 (dd, J = 13.3, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 147.4 (d, $J_{C\text{-}F}$= 245.3 Hz), 136.5, 132.6, 130.0, 128.8 (d, $J_{C\text{-}F}$= 8.2 Hz), 128.5, 127.6, 127.5, 123.9 (d, $J_{C\text{-}F}$= 6.0 Hz), 120.8, 120.0 (d, $J_{C\text{-}F}$= 3.0 Hz), 117.7 (d, $J_{C\text{-}F}$= 20.2 Hz), 76.0 (d, $J_{C\text{-}F}$= 2.2 Hz), 45.3 (d, $J_{C\text{-}F}$= 4.5 Hz), 43.1. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{minor} =

12.5 min, t_{major} = 15.6 min; ee = 93%., $[\alpha]_D^{25}$ –21.0 (c 1.00, $CHCl_3$). FTIR (neat): υ 3390, 1705, 1632, 1488, 1473, 1348, 1247, 1189, 1159, 1079, 995, 923, 791, 751, 730, 698, 666 cm^{-1}. HRMS (CI) Calcd. for $C_{18}H_{17}FNO_2$ (M+1): 298.1243, Found: 298.1241. mp (DCM/Hexane) 126-127 ^oC, White solid

^1H NMR

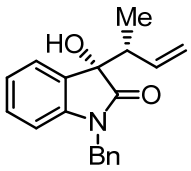


^{13}C NMR



Pocedure for Enantioselective Crotylation of Isatins 1a-1f and Spectral Data for Adducts 3.20a-3.20f

(*S*)-1-benzyl-3-((*R*)-but-3-en-2-yl)-3-hydroxyindolin-2-one



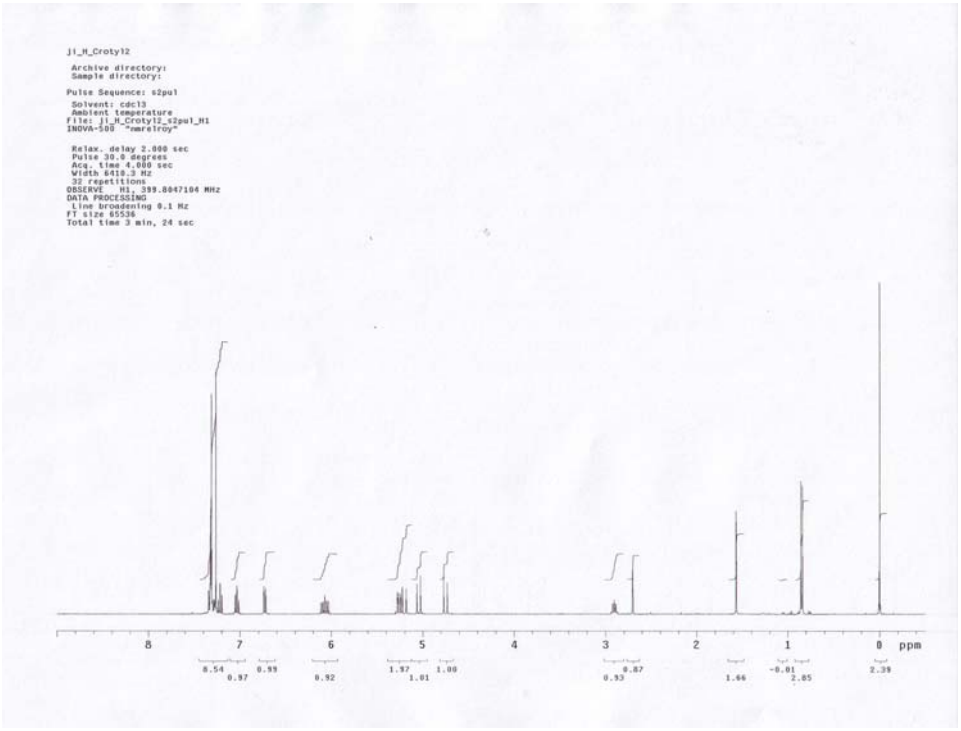
3.20a

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzylindoline-2,3-dione **3.18a** (46.9 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$

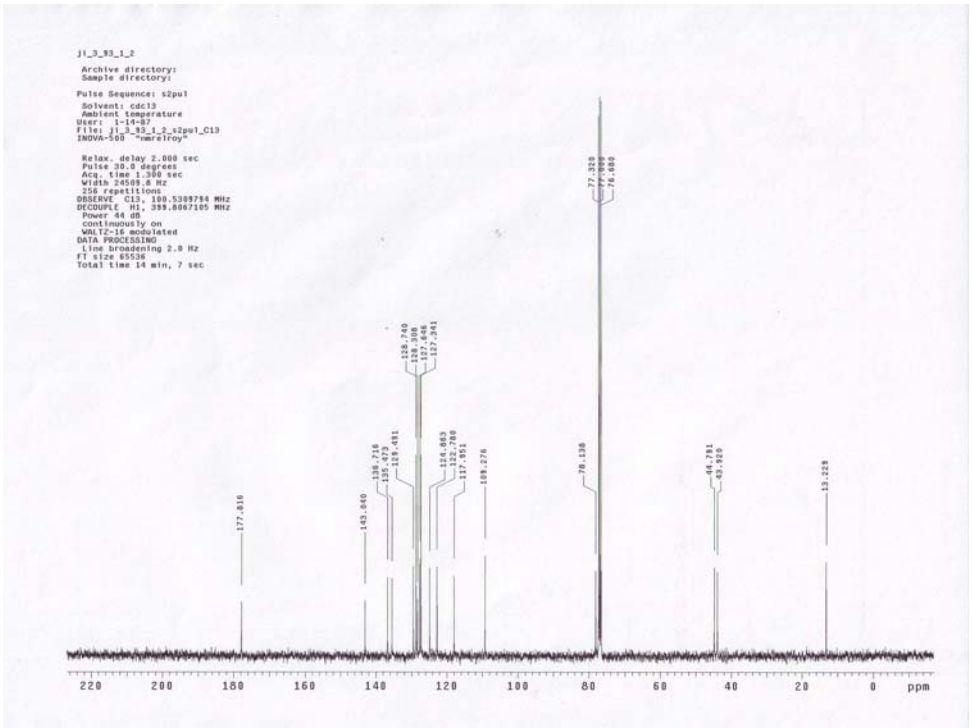
(3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (6.5 mg, 0.02 mmol, 10 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (51 μL, 0.40 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20) provided **3.20a** (48.7 mg, 0.166 mmol, *anti*:*syn*=13:1) as a white solid in 83% yield.

TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.19 (m, 6H), 7.03 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.73 (d, *J* = 6.73 Hz, 1H), 6.12-6.03 (m, 1H), 5.28-5.18 (m, 2H), 5.04 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.7 Hz, 1H), 2.94-2.87 (m, 1H), 2.71 (brs, 1H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.8, 143.0, 136.7, 135.5, 129.5, 128.7, 128.3, 127.6, 127.3, 124.9, 122.8, 118.0, 109.3, 78.1, 44.8, 43.9, 13.2. HPLC: (Chiralpak AD-H + OJ-H column, hexanes:*i*-PrOH =95:5, 0.8 mL/min, 210 nm), t_{minor} = 50.3 min, t_{major} = 61.3 min; ee = 80%. FTIR (neat): υ 3361, 2956, 1698, 1613, 1492, 1467, 1454, 1432, 1372, 1358, 1283, 1182, 1122, 1098, 1078, 1045, 1005, 954, 924, 753, 722, 694, 660 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{20}NO_2$ (M+1): 294.1494, Found: 294.1496.

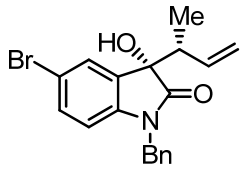
^{1}H NMR



^{13}C NMR



(*S*)-1-benzyl-5-bromo-3-((*R*)-but-3-en-2-yl)-3-hydroxyindolin-2-one



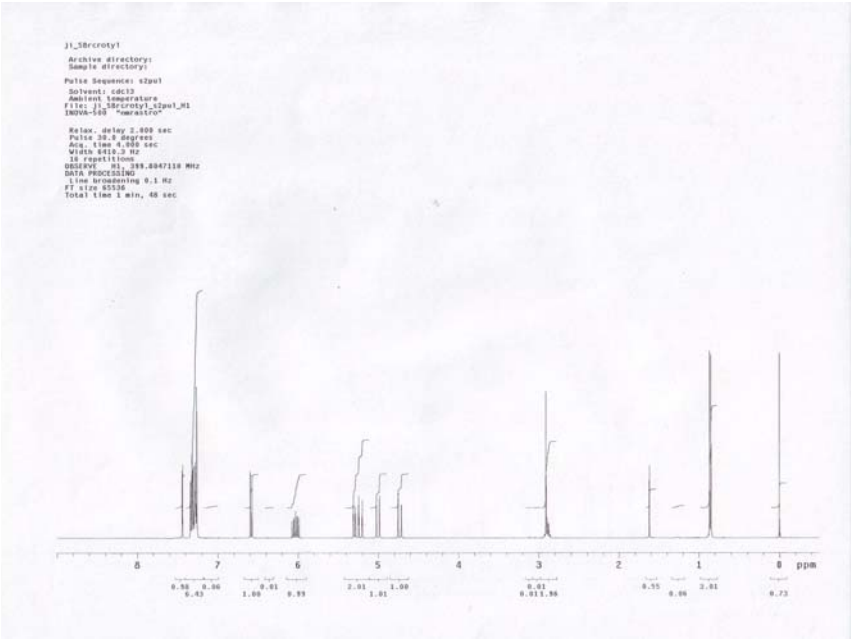
3.20b

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-5-bromoindoline-2,3-dione **3.18b** (62.6 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 5 mol%), CTH-(*R*)-P-PHOS (12.9 mg, 0.02 mmol, 10 mol%), 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 20 mol%), Cs_2CO_3 (13.0 mg, 0.04 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (51 μL, 0.40 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^oC for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:30 to 1:20) provided **3.20b** (53.6 mg, 0.144 mmol, *anti*:*syn*=16:1) as a white solid in 72% yield.

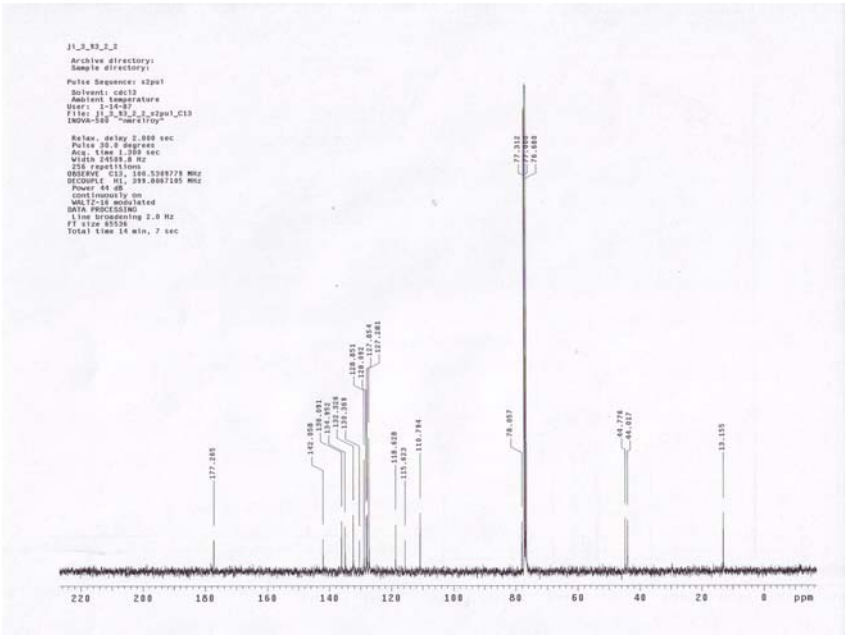
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 10:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 1.8 Hz, 1H), 7.34-7.25 (m, 6H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.08-5.99 (m, 1H), 5.31-5.28 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.73 (d, *J* = 15.7 Hz, 1H), 2.93-2.86 (m, 1H), 2.91 (brs, 1H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.3, 142.1, 136.1, 135.0, 132.3, 130.4, 128.9, 128.1, 127.9, 127.3, 118.6, 115.6, 110.8, 78.1, 44.8, 44.0, 13.2. HPLC: (Chiralpak OJ-H column, hexanes:*i*-PrOH = 93:7, 1.0 mL/min, 254

nm), t_{minor} = 10.0 min, t_{major} = 20.5 min; ee = 86%. FTIR (neat): υ 3300, 2972, 1693, 1611, 1483, 1368, 1338, 1173, 1078, 908, 821, 742, 698, 655 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{20}BrNO_2$: 371.0521, Found: 371.0521.

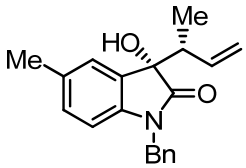
^{1}H NMR



^{13}C NMR



(*S*)-1-benzyl-3-((*R*)-but-3-en-2-yl)-3-hydroxy-5-methylindolin-2-one



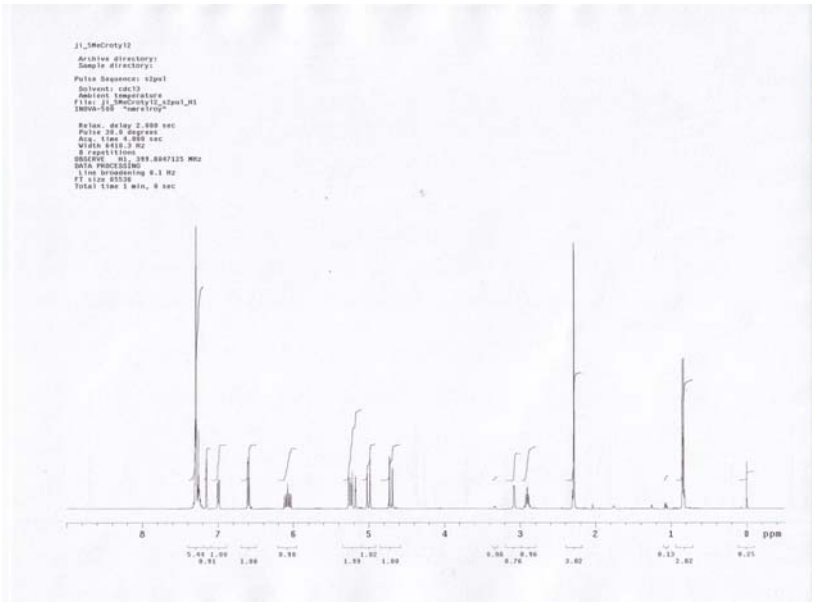
3.20c

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-5-methylindoline-2,3-dione **3.18c** (50.2 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.03 mmol, 20 mol%) and 2-methyl THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (51 μL, 0.40 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.20c** (49.8 mg, 0.162 mmol, *anti*:*syn*=18:1) as a white solid in 81% yield.

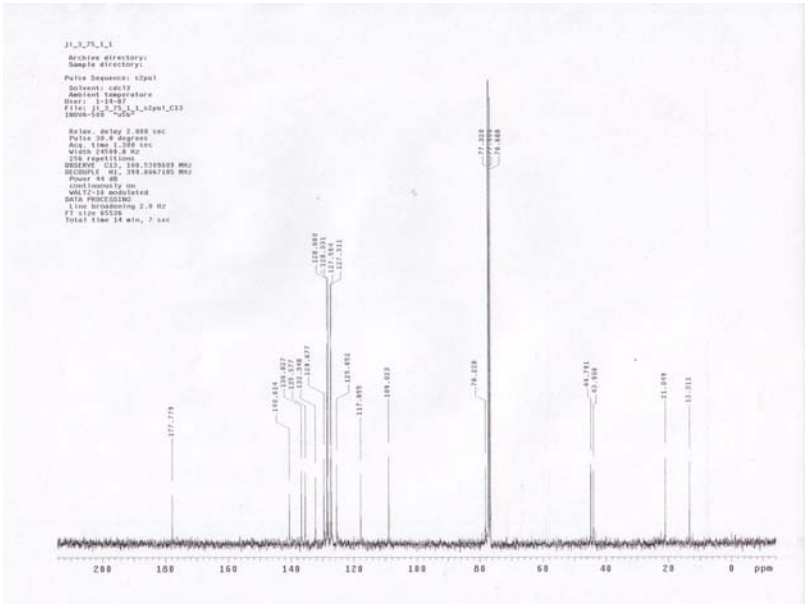
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 10:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.21 (m, 5H), 7.15 (s, 1H), 7.01-6.98 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.12-6.03 (m, 1H), 5.27-5.18 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 15.7 Hz, 1H), 3.08 (brs, 1H), 2.94-2.87 (m, 1H), 2.29 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 140.6, 136.8, 135.6, 132.3, 129.7, 128.7, 128.3, 127.6, 127.3, 125.7, 117.9, 109.0, 78.2, 44.8, 43.9, 21.0, 13.3. HPLC: (Chiralpak AD-H + OD-H column,

hexanes:*i*-PrOH = 95:5, 0.4 mL/min, 254 nm), t_{minor} = 100.5 min, t_{major} = 104.8 min; ee = 89%. FTIR (neat): υ 3341, 2924, 1693, 1624, 1603, 1495, 1454, 1414, 1374, 1352, 1195, 1155, 1134, 810, 729, 696 cm^{-1}.HRMS (CI) Calcd. for $C_{20}H_{21}NO_2$: 307.1572, Found: 307.1577.

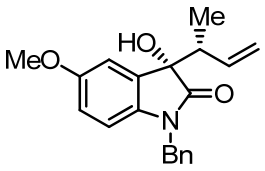
^{1}H NMR



^{13}C NMR



(*S*)-1-benzyl-3-((*R*)-but-3-en-2-yl)-3-hydroxy-5-methoxyindolin-2-one



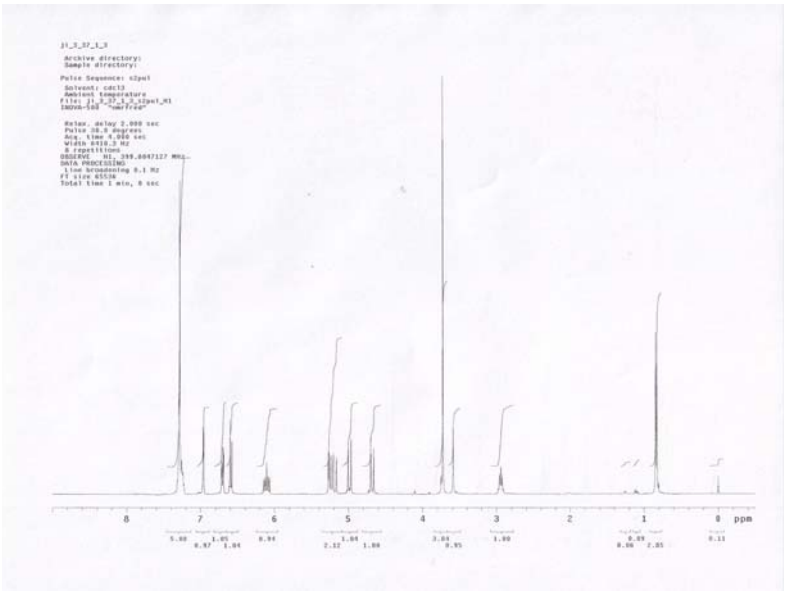
3.20d

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-5-methoxyindoline-2,3-dione **3.18d** (52.3 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (13.0 mg, 0.03 mmol, 20 mol%) and 2-methyl THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (51 μL, 0.40 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.20d** (56.3 mg, 0.174 mmol, *anti*:*syn*=29:1) as a white solid in 87% yield.

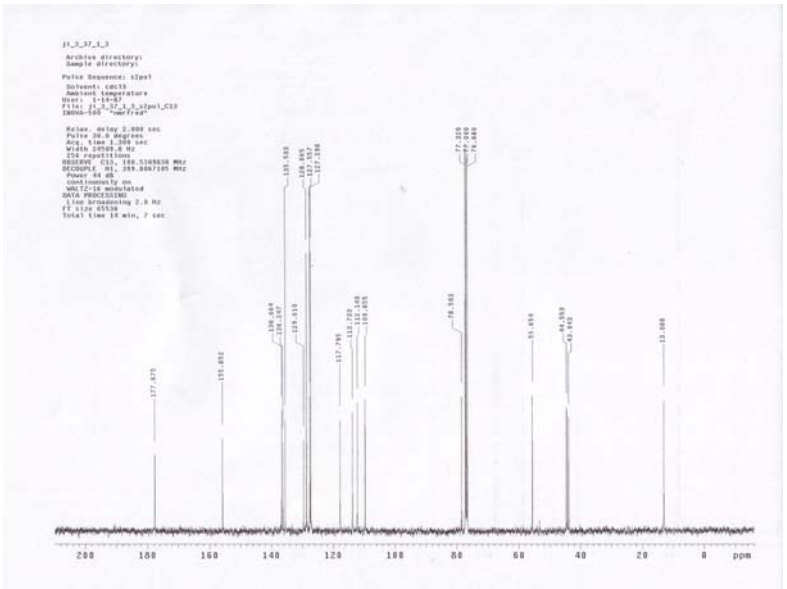
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 8:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.15-6.07 (m, 1H), 5.26-5.16 (m, 2H), 4.98 (d, *J* = 15.7 Hz, 1H), 4.68 (d, *J* = 15.7 Hz, 1H), 3.72 (s, 3H), 3.59 (brs, 1H), 2.98-2.91 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 155.9, 136.7, 136.2, 135.5, 129.6, 128.7, 127.6, 127.3, 117.8, 113.7, 112.1, 109.7, 78.5, 55.7, 44.6, 43.9, 13.1. HPLC: (Chiralcel OJ-H column,

hexanes:*i*-PrOH = 93:7, 1.0 mL/min, 254 nm), t_{minor} = 15.1 min, t_{major} = 30.5 min; ee = 92%. FTIR (neat): υ 3383, 2969, 1695, 1603, 1488, 1455, 1435, 1371, 1346, 1269, 1199, 1179, 1079, 1042, 1014, 955, 912, 878, 805, 782, 729, 697 cm^{-1}. HRMS (CI) Calcd. for $C_{20}H_{21}NO_3$: 323.3856, Found: 323.1521.

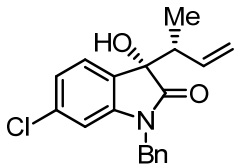
^{1}H NMR



^{13}C NMR



(*S*)-1-benzyl-3-((*R*)-but-3-en-2-yl)-6-chloro-3-hydroxyindolin-2-one



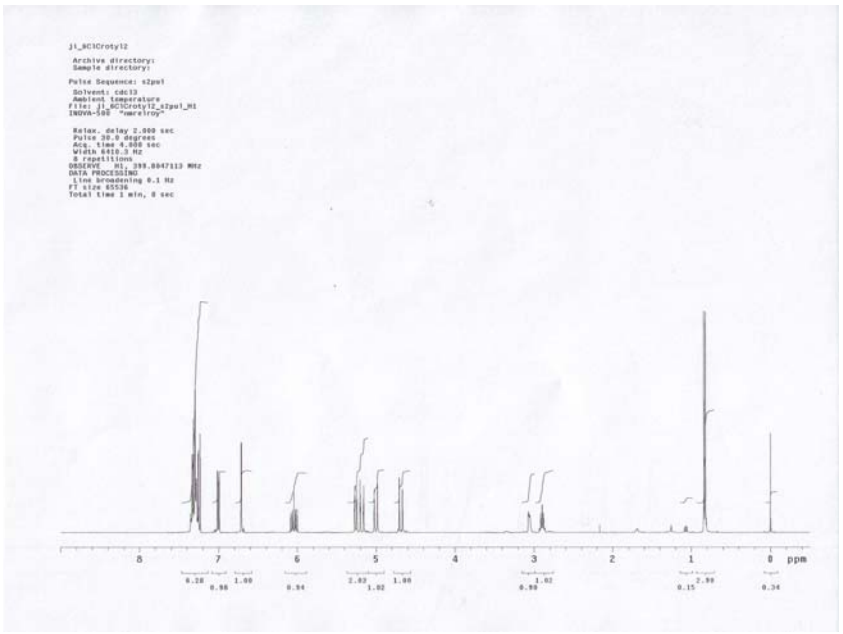
3.20e

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-6-chloroindoline-2,3-dione **3.18e** (53.5 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (6.5 mg, 0.02 mmol, 10 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (51 μL, 0.40 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20 to 1:10) provided **3.20e** (45.9 mg, 0.140 mmol, *anti*:*syn*=19:1) as a colorless oil in 70% yield.

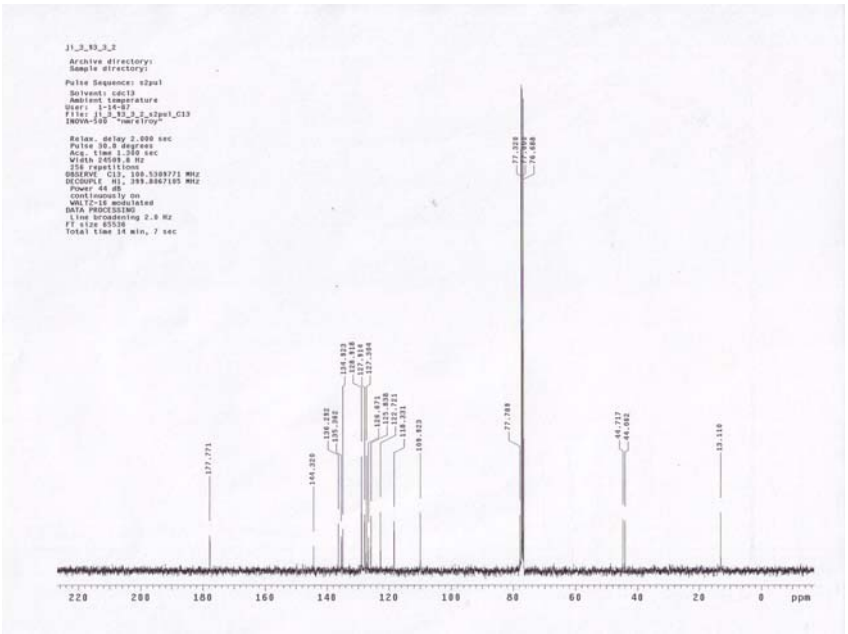
TLC (SiO_2): R_f = 0.24 (toluene:ethyl acetate, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.23 (m, 6H), 7.00 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 6.09-6.00 (m, 1H), 5.28-5.16 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.69 (d, *J* = 15.7 Hz, 1H), 3.07 (brs, 1H), 2.93-2.86 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 144.3, 136.3, 135.4, 134.9, 128.9, 127.9, 127.3, 126.7, 125.8, 122.7, 118.3, 109.9, 77.8, 44.7, 44.1, 13.1. HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min,

254 nm), t_{minor} = 27.7 min, t_{major} = 42.9 min; ee = 91%. FTIR (neat): υ 3393, 2973, 1708, 1609, 1455, 1488, 1438, 1373, 1351, 1174, 1113, 1072, 954, 920, 875, 843, 813, 758, 728, 699 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{18}ClNO_2$: 328.1104, Found: 328.1107.

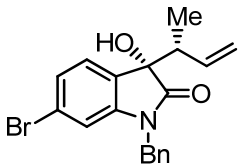
^{1}H NMR



^{13}C NMR



(*S*)-1-benzyl-6-bromo-3-((*R*)-but-3-en-2-yl)-3-hydroxyindolin-2-one



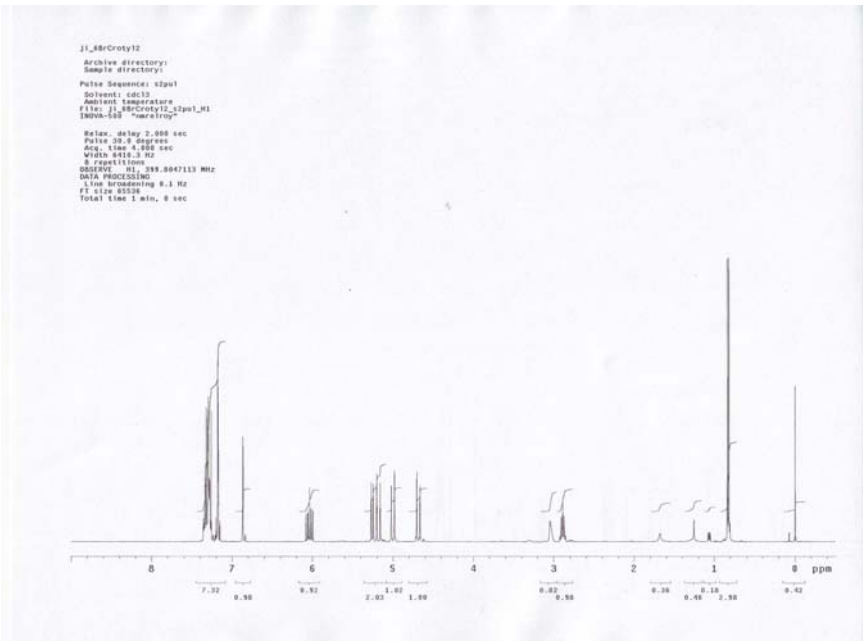
3.20f

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-6-bromoindoline-2,3-dione **3.18f** (63.1 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 5 mol%), CTH-(*R*)-P-PHOS (12.9 mg, 0.02 mmol, 10 mol%), 4-cyano-3-nitrobenzoic acid (7.7 mg, 0.04 mmol, 20 mol%), Cs_2CO_3 (13.0 mg, 0.04 mmol, 20 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (51 μL, 0.40 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:30 to 1:20) provided **3.20f** (60.3 mg, 0.162 mmol, *anti*:*syn*=15:1) as a colorless oil in 81% yield.

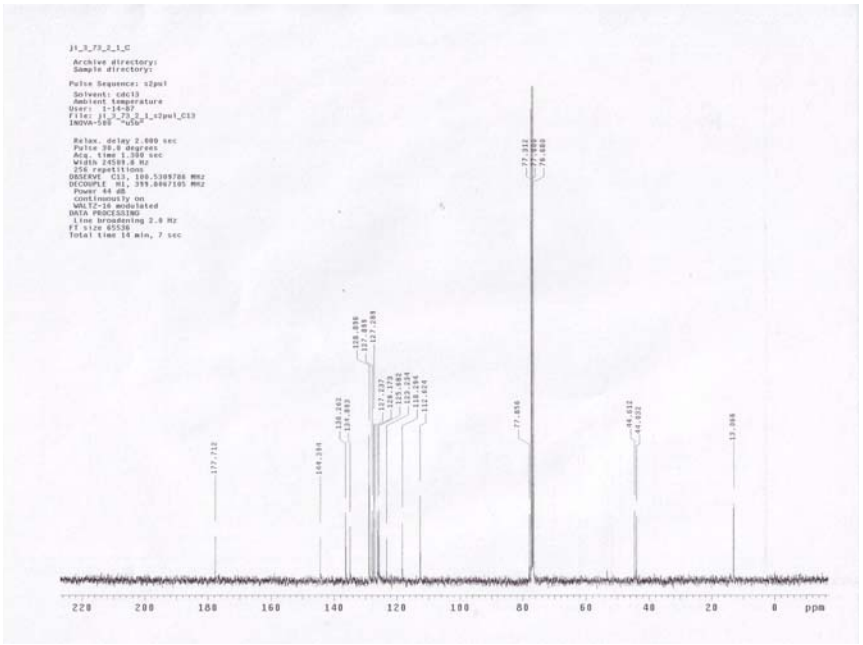
TLC (SiO_2): R_f = 0.25 (toluene:ethyl acetate, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.17 (m, 7H), 6.87-6.86 (m, 1H), 6.08-5.99 (m, 1H), 5.28-5.15 (m, 2H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.68 (d, *J* = 15.7 Hz, 1H), 3.05 (brs, 1H), 2.93-2.86 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 144.4, 136.3, 134.9, 128.9, 127.9, 127.3, 127.2, 126.2, 125.7, 123.2, 118.3, 112.6, 77.9, 44.6, 44.0, 13.1. HPLC: (Chiralpak AS-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 34.5 min, t_{major} =

61.2 min; ee = 89%. FTIR (neat): υ 3392, 2971, 1707, 1604, 1485, 1455, 1429, 1373, 1350, 1174, 1127, 1079, 1061, 1039, 997, 953, 909, 869, 727, 698 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{19}BrNO_2$ (M+1): 372.0599, Found: 372.0599.

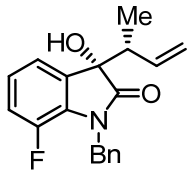
^{1}H NMR



^{13}C NMR



(*S*)-1-benzyl-3-((*R*)-but-3-en-2-yl)-7-fluoro-3-hydroxyindolin-2-one



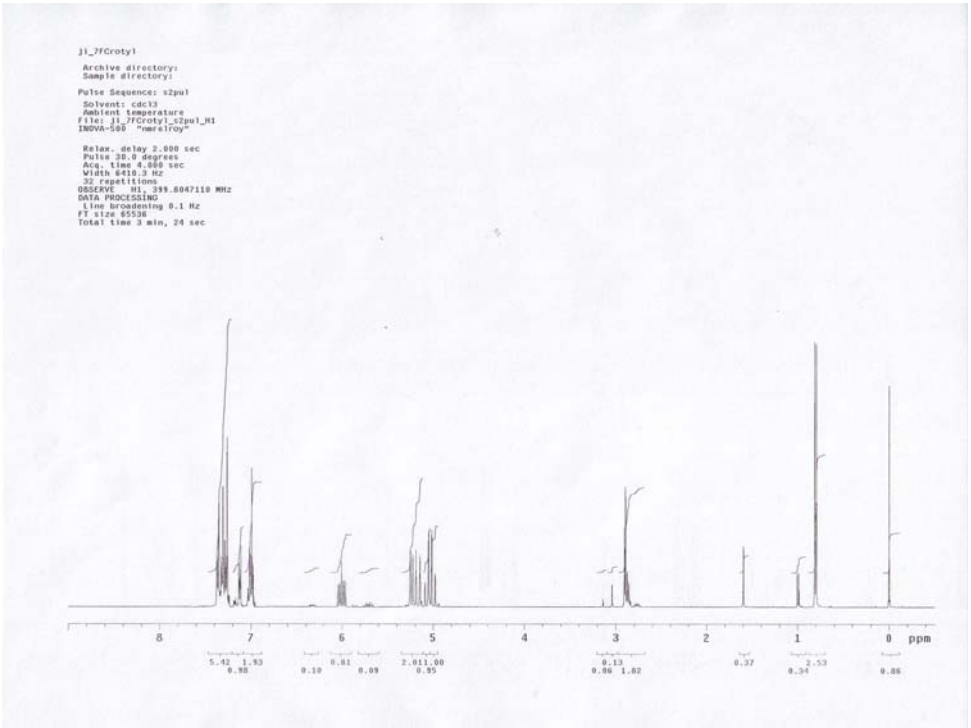
3.20g

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 1-benzyl-7-fluoroindoline-2,3-dione **3.18g** (50.7 mg, 0.20 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (6.5 mg, 0.010 mmol, 5 mol%), 4-cyano-3-nitrobenzoic acid (3.9 mg, 0.020 mmol, 10 mol%), Cs_2CO_3 (6.5 mg, 0.02 mmol, 10 mol%) and THF (2.0 mL, 0.1 M). The mixture was stirred at the ambient temperature for 0.5 hr. Isopropanol (62 μL, 0.805 mmol, 400 mol%) and acetic acid 3-buten-2-yl ester (101 μL, 0.80 mmol, 400 mol%) were added and the reaction mixture was allowed to stir at 100 ^{o}C for 72 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the product by column chromatography (SiO_2; ethyl acetate:toluene, 1:20) provided **3.20g** (39.9 mg, 0.128 mmol, *anti*:*syn*=19:1) as a white solid in 64% yield.

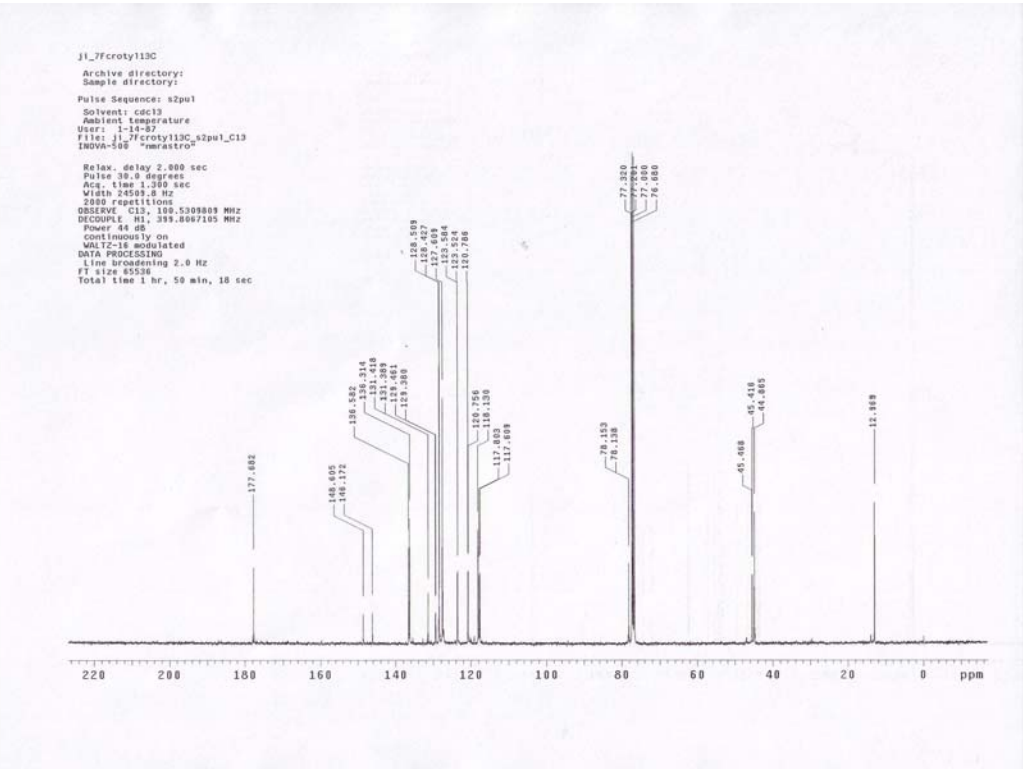
TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 7.13-7.11 (m, 1H), 7.04-6.96 (m, 2H), 6.05-5.96 (m, 1H), 5.25-5.14 (m, 2H), 5.07 (d, J = 15.4 Hz, 1H), 4.99 (d, J = 15.4 Hz, 1H), 2.91-2.84 (m, 1H), 2.90 (brs, 1H), 0.80 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 147.4 (d, $J_{C\text{-}F}$= 244.6 Hz), 136.4 (d, $J_{C\text{-}F}$= 26.9 Hz), 131.4 (d, $J_{C\text{-}F}$= 3.0 Hz), 129.4 (d, $J_{C\text{-}F}$= 8.2 Hz), 128.5, 127.6, 123.6 (d, $J_{C\text{-}F}$= 6.0 Hz), 120.8 (d, $J_{C\text{-}F}$= 3.0 Hz), 118.1, 117.7 (d, $J_{C\text{-}F}$= 19.4

Hz), 78.1 (d, $J_{C\text{-}F}$= 1.5 Hz), 45.4 (d, $J_{C\text{-}F}$= 5.2 Hz), 44.9, 13.0. HPLC: (Chiralpak OJ-H column, hexanes:*i*-PrOH = 97:3, 1.0 mL/min, 254 nm), t_{minor} = 20.7 min, t_{major} = 24.5 min; ee = 85%. FTIR (neat): υ 3374, 2975, 1704, 1632, 1358, 1255, 1236, 1201, 1166, 787, 741, 731, 717, 695 cm^{-1}. HRMS (CI) Calcd. for $C_{19}H_{19}FNO_2$ (M+1): 312.1400, Found: 312.1398.

^{1}H NMR



^{13}C NMR

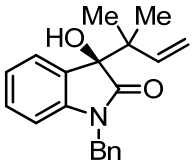


General Pocedure for Enantioselective Reverse Prenylation of Isatins

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with $[Ir(cod)Cl]_2$ (5.0 mg, 0.0075 mmol, 2.5 mol%), CTH-(*R*)-P-PHOS (9.7 mg, 0.015 mmol, 5 mol%), 3-nitrobenzoic acid (3.8 mg, 0.0225 mmol, 7.5 mol%), Cs_2CO_3 (7.3 mg, 0.0225 mmol, 7.5 mol%) and toluene (0.3 mL, 1.0 M). The mixture was stirred at 80 ^oC for 0.5 hr. Isatin (0.30 mmol, 100 mol%), 1,1-dimethylallene (59 μL, 0.6 mmol, 200 mol%) and Isopropanol (46 μL, 0.6 mmol, 200 mol%) were added and the reaction mixture was allowed to stir at 60 ^oC for 40 hr, at which point the reaction mixture was

concentrated *in vacuo*. Purification of the product by column chromatography provided the corresponding product.

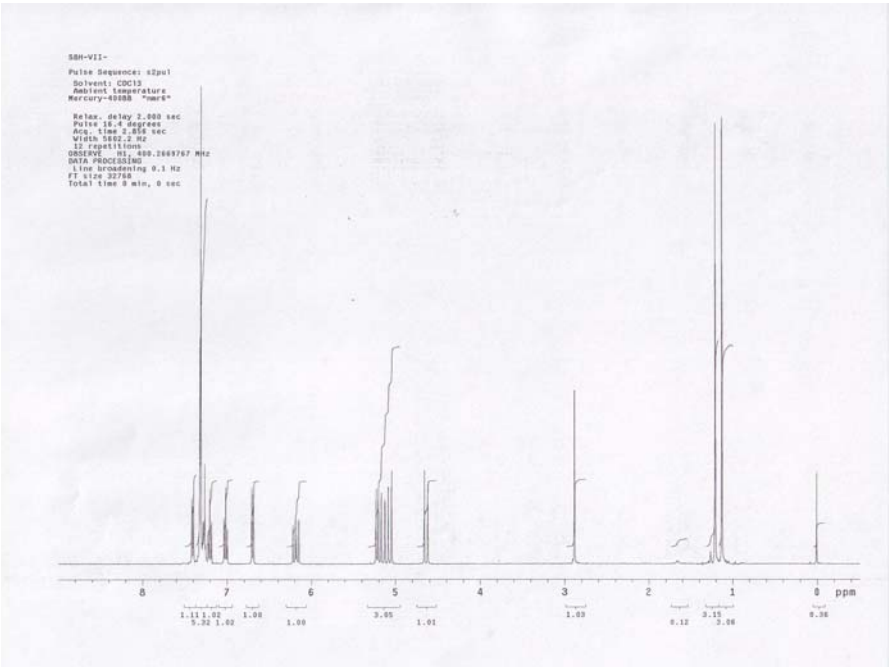
(*R*)-1-benzyl-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one



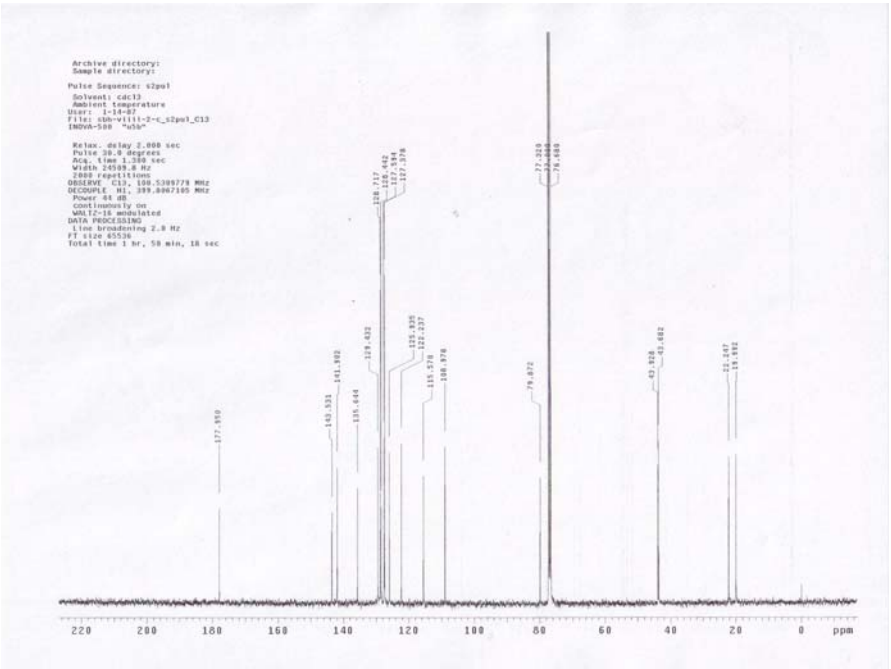
3.21a

TLC (SiO_2): R_f = 0.25 (toluene:ethyl acetate, 30:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.34-7.24 (m, 5H), 7.20 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.02 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.19 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.22 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.15 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.07 (d, *J* = 15.7 Hz, 1H), 4.64 (d, *J* = 15.7 Hz, 1H), 2.89 (brs, 1H), 1.21 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 143.5, 141.9, 135.6, 129.4, 128.7, 128.4, 127.6, 127.4, 125.9, 122.2, 115.6, 109.0, 79.9, 43.9, 43.7, 22.2, 20.0. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{major} = 9.1 min, t_{minor} = 12.7 min; ee = 96%., $[\alpha]_D^{25}$ +139.6 (c 1.01, $CHCl_3$). FTIR (neat): υ 3396, 3063, 2970, 2923, 1690, 1608, 1487, 1466, 1411, 1372, 1341, 1260, 1188, 1156, 1122, 1096, 1079, 1050, 1027, 966, 950, 926, 907, 860, 847, 800, 756, 746, 724, 694, 669 cm^{-1}. HRMS (CI) Calcd. for $C_{20}H_{22}NO_2$ (M+1): 308.1651, Found: 308.1650. mp (DCM/Hexane) 83-84 ^oC, White solid.

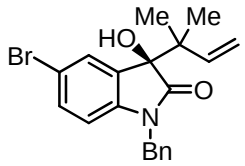
^{1}H NMR



^{13}C NMR



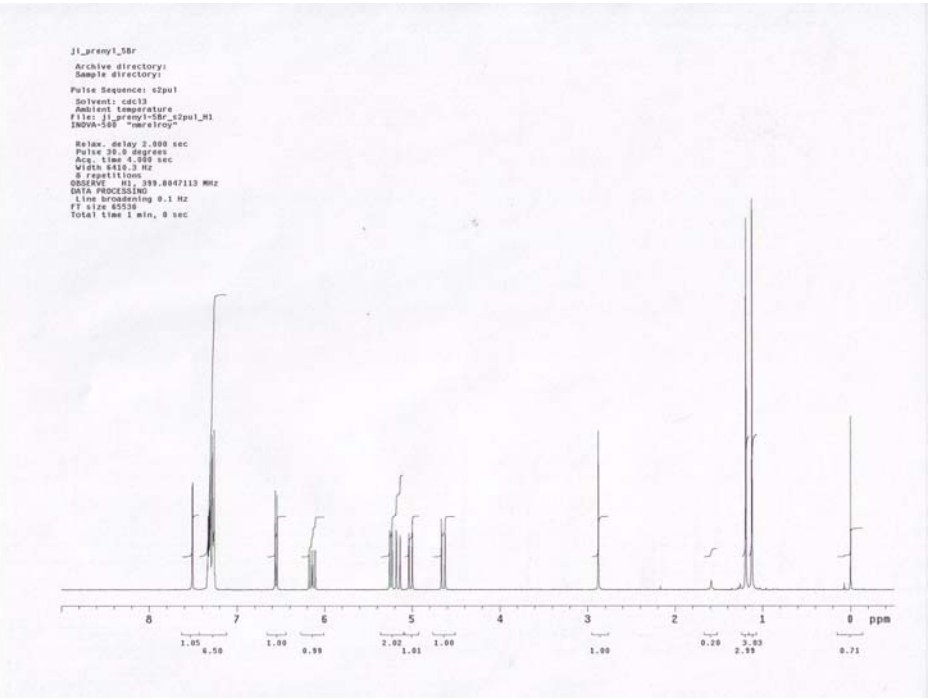
(*R*)-1-benzyl-5-bromo-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one



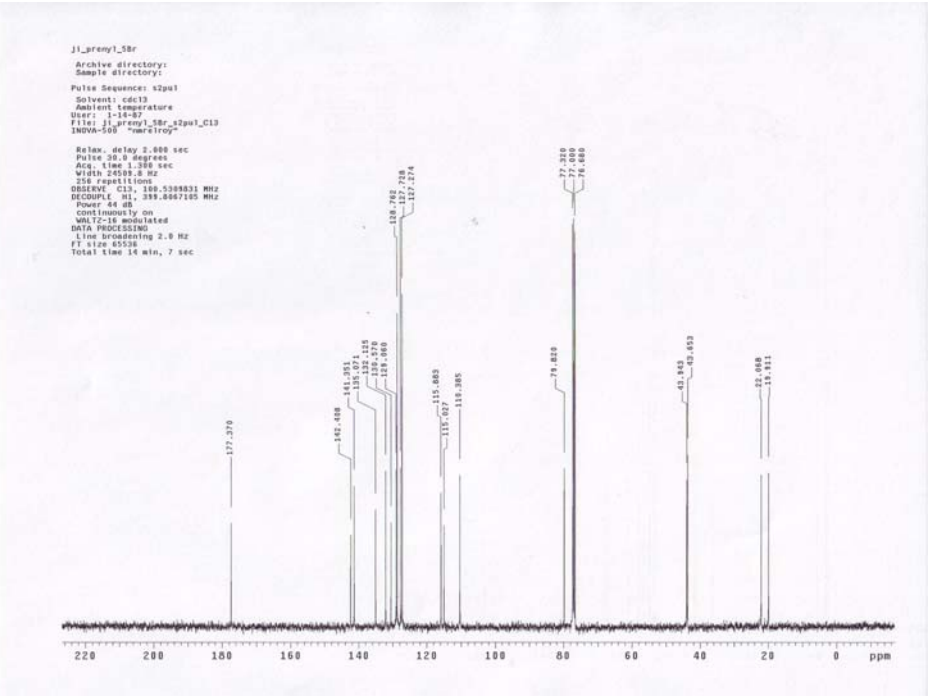
3.21b

TLC (SiO_2): R_f = 0.3 (toluene:ethyl acetate, 30:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.34-7.25 (m, 6H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.14 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.24 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.16 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.02 (d, *J* = 15.7 Hz, 1H), 4.65 (d, *J* = 15.7 Hz, 1H), 2.88 (brs, 1H), 1.19 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 142.4, 141.4, 135.1, 132.1, 130.6, 129.1, 128.8, 127.7, 127.3, 115.9, 115.0, 110.4, 79.8, 43.9, 43.7, 22.1, 19.9. HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 254 nm), t_{major} = 9.0 min, t_{minor} = 15.2 min; ee = 90%., $[\alpha]_D^{26}$ +78.9 (c 1.00, $CHCl_3$) FTIR (neat): υ 3377, 2969, 1689, 1601, 1495, 1479, 1455, 1446, 1427, 1377, 1360, 1345, 1180, 1159, 1131, 1106, 1065, 1043, 1029, 1018, 1006, 949, 918, 878, 854, 803, 748, 742, 728, 717, 697, 675 cm^{-1}. HRMS (CI) Calcd. for $C_{20}H_{21}BrNO_2$ (M+1): 386.0747, Found: 386.0750. mp (DCM/Hexane) 144-145 ^oC, White solid.

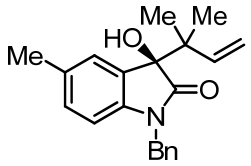
^{1}H NMR



^{13}C NMR



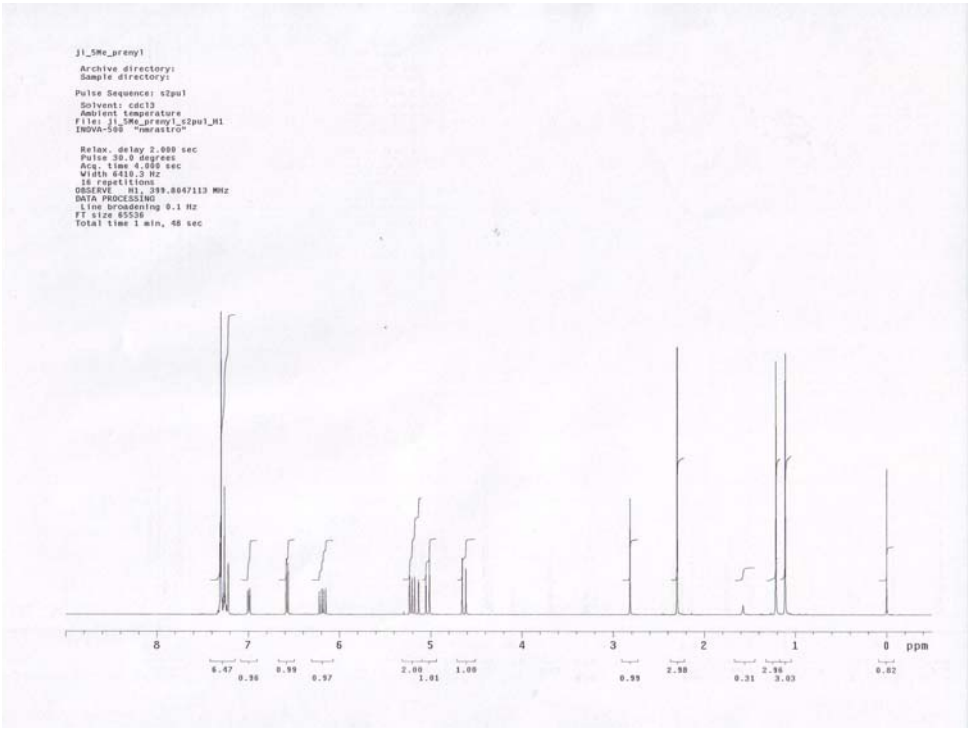
(*R*)-1-benzyl-3-hydroxy-5-methyl-3-(2-methylbut-3-en-2-yl)indolin-2-one



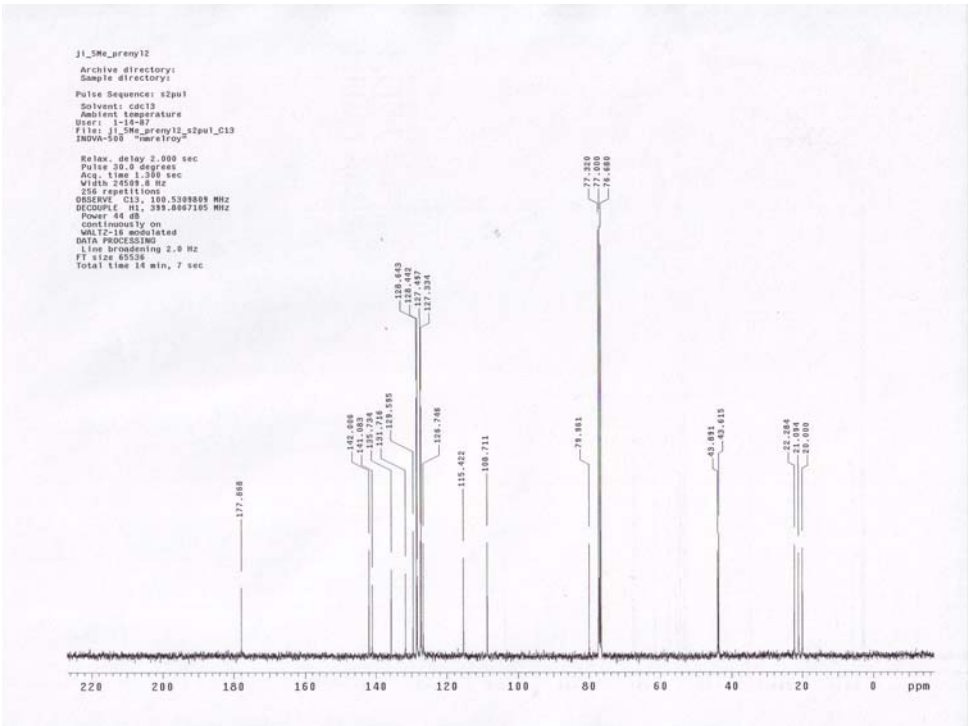
3.21c

TLC (SiO_2): R_f = 0.25 (toluene:ethyl acetate, 30:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.22 (m, 6H), 7.04-6.98 (m, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.19 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.22 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.15 (dd, *J* = 17.5, 1.2 Hz, 1H), 5.03 (d, *J* = 15.7 Hz, 1H), 4.64 (d, *J* = 15.7 Hz, 1H), 2.82 (brs, 1H), 2.30 (s, 3H), 1.21 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 142.0, 141.1, 135.7, 131.7, 129.6, 128.6, 128.4, 127.5, 127.3, 126.7, 115.4, 108.7, 80.0, 43.9, 43.6, 22.3, 21.1, 20.0. HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{major} = 7.7 min, t_{minor} = 9.7 min; ee = 93%., $[\alpha]_D^{25}$ +83.9 (c 1.38, $CHCl_3$). FTIR (neat): υ 3378, 2967, 2915, 1688, 1617, 1602, 1496, 1469, 1455, 1412, 1379, 1363, 1347, 1198, 1178, 1103, 1053, 1031, 1018, 1006, 975, 949, 924, 911, 884, 805, 776, 749, 743, 723, 696, 683, 664 cm^{-1}. HRMS (CI) Calcd. for $C_{21}H_{23}NO_2$: 321.1729, Found: 321.1729. mp (DCM/Hexane) 109-110 ^oC, White solid.

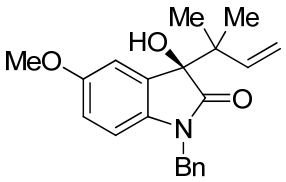
^{1}H NMR



^{13}C NMR



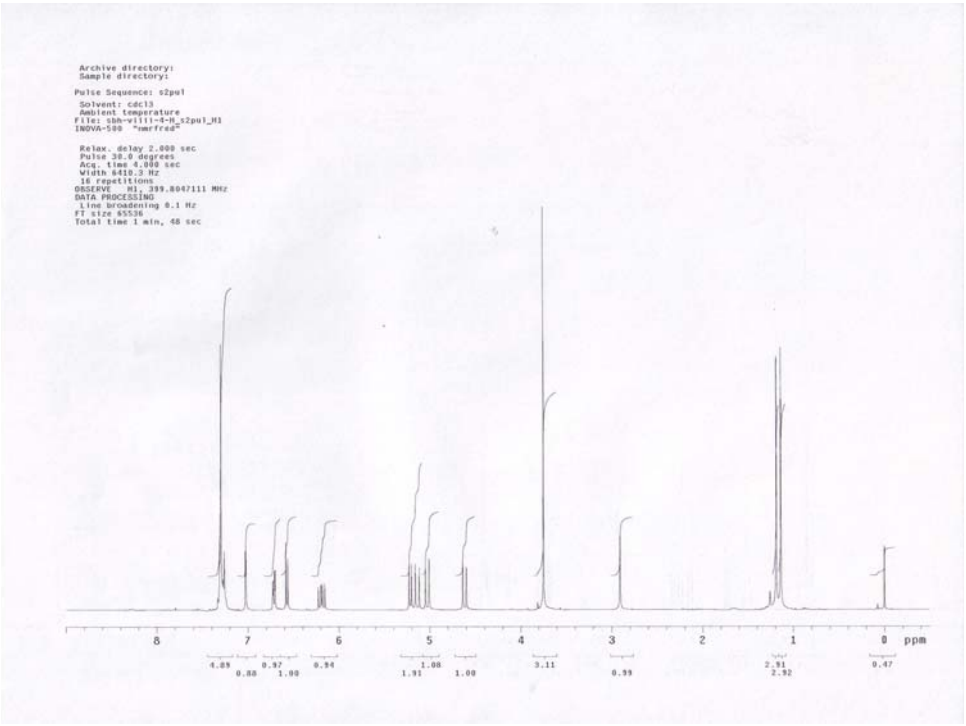
(*R*)-1-benzyl-3-hydroxy-5-methoxy-3-(2-methylbut-3-en-2-yl)indolin-2-one



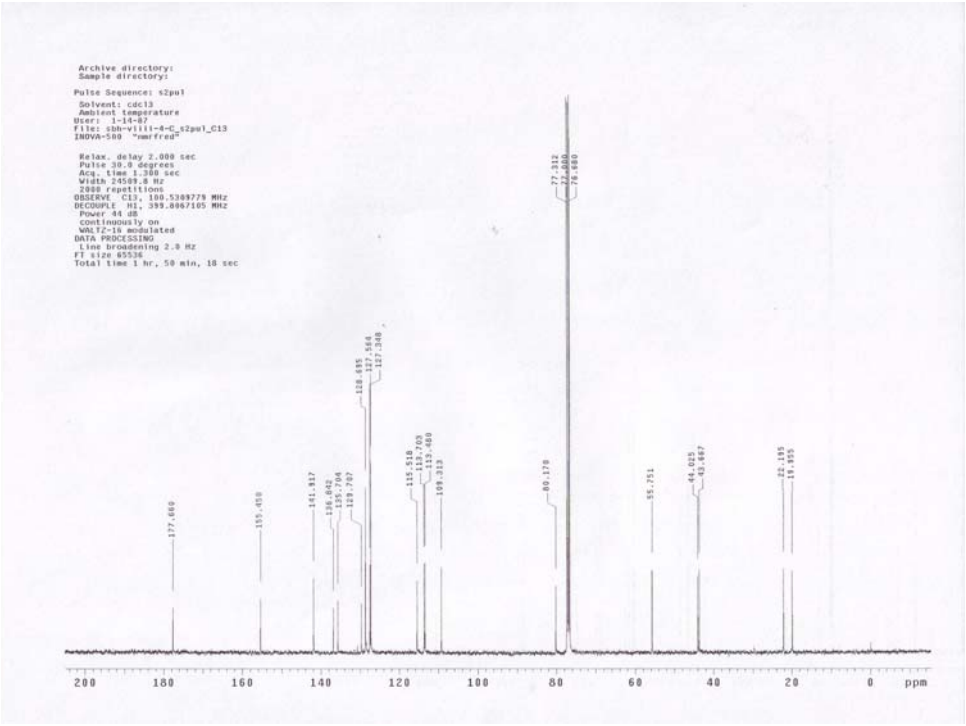
3.21d

TLC (SiO_2): R_f = 0.30 (toluene:ethyl acetate, 30:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.19 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.22 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.14 (dd, *J* = 17.5, 1.2 Hz, 1H), 5.03 (d, *J* = 15.7 Hz, 1H), 4.62 (d, *J* = 15.7 Hz, 1H), 3.75 (s, 3H), 2.91 (brs, 1H), 1.19 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 155.5, 141.9, 136.8, 135.7, 129.7, 128.7, 127.6, 127.3, 115.5, 113.7, 113.5, 109.3, 80.2, 55.8, 44.0, 43.7, 22.2, 20.0. HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 254 nm), t_{major} = 10.5 min, t_{minor} = 12.2 min; ee = 96%. $[\alpha]_D^{26}$ +97.2 (c 1.00, $CHCl_3$). FTIR (neat): υ 3409, 2926, 1687, 1489, 1457, 1443, 1390, 1375, 1364, 1350, 1313, 1295, 1203, 1181, 1150, 1101, 1082, 1050, 1035, 1019, 1003, 970, 949, 926, 917, 869, 802, 772, 749, 741, 728, 696 cm^{-1}. HRMS (CI) Calcd. for $C_{21}H_{23}NO_3$: 337.1678, Found: 337.1683. mp (DCM/Hexane) 99-100 ^oC, White solid

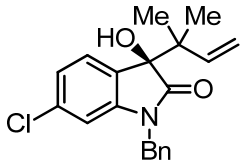
^{1}H NMR



^{13}C NMR



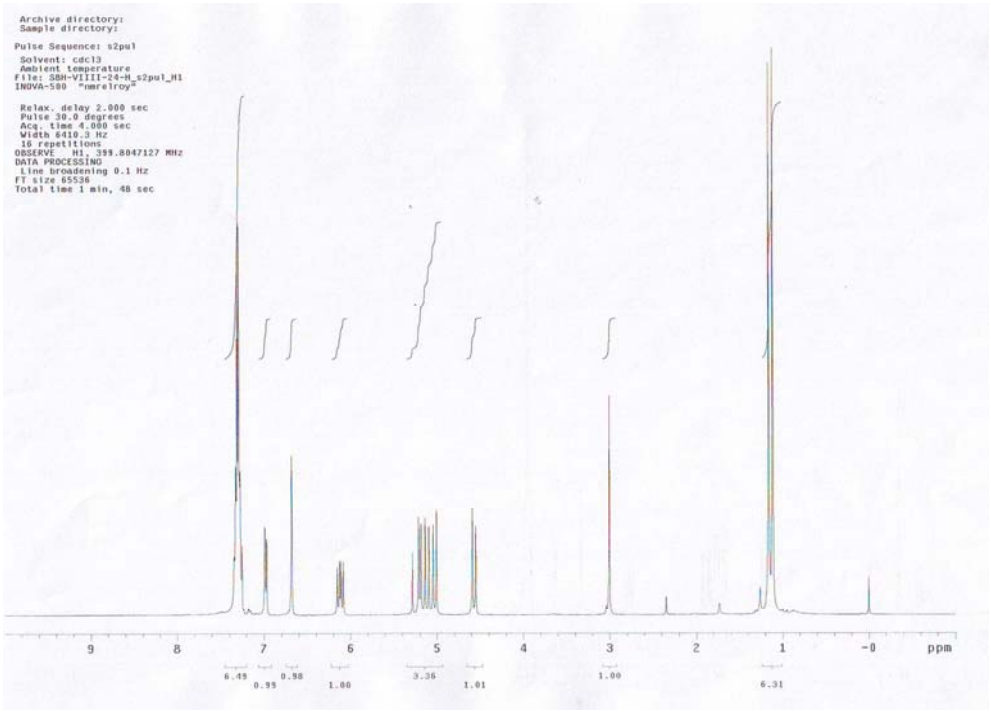
(*R*)-1-benzyl-6-chloro-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one



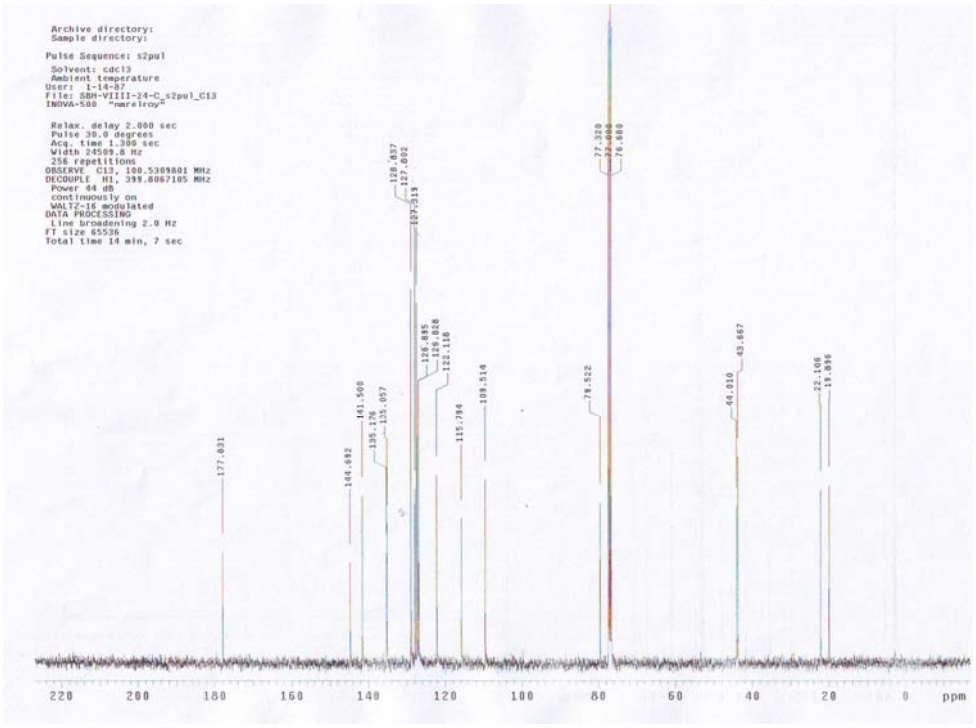
3.21e

TLC (SiO_2): R_f = 0.30 (toluene:ethyl acetate, 30:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 6H), 6.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.68 (d, *J* = 1.2 Hz, 1H), 6.12 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 5.12 (d, *J* = 17.6 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.57 (d, *J* = 15.6 Hz, 1H), 3.00 (s, 1H), 1.16 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 144.7, 141.5, 135.2, 135.1, 128.8, 127.8, 127.3, 126.9, 126.8, 122.1, 115.8, 109.5, 79.5, 44.0, 43.7, 22.1, 19.9. HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{major} = 12.2 min, t_{minor} = 15.8 min; ee = 93%., $[\alpha]_D^{26}$ +98.2 (c 1.43, $CHCl_3$). FTIR (neat): υ 3434, 2969, 2360, 1710, 1606, 1488, 1455, 1438, 1414, 1341, 1169, 1119, 1075, 959, 919, 868, 840, 817, 739, 722, 697 cm^{-1}. HRMS (CI) Calcd. for $C_{20}H_{21}NO_2Cl$ $(M+H)^+$: 342.1261 Found: 342.1263.

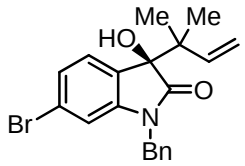
^{1}H NMR



^{13}C NMR



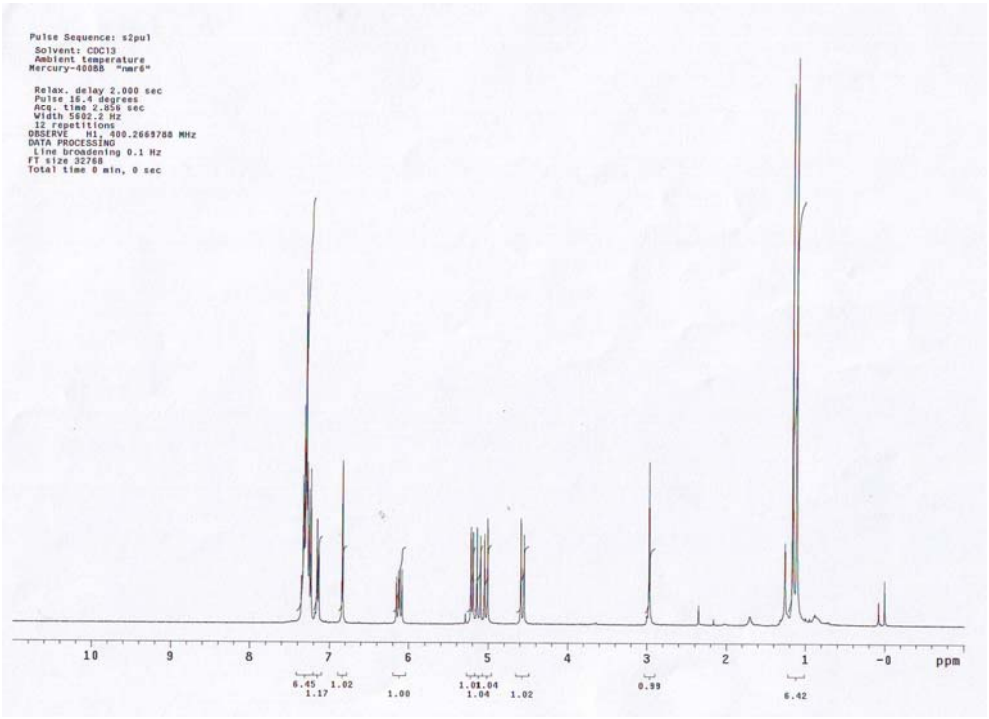
(*R*)-1-benzyl-6-bromo-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one



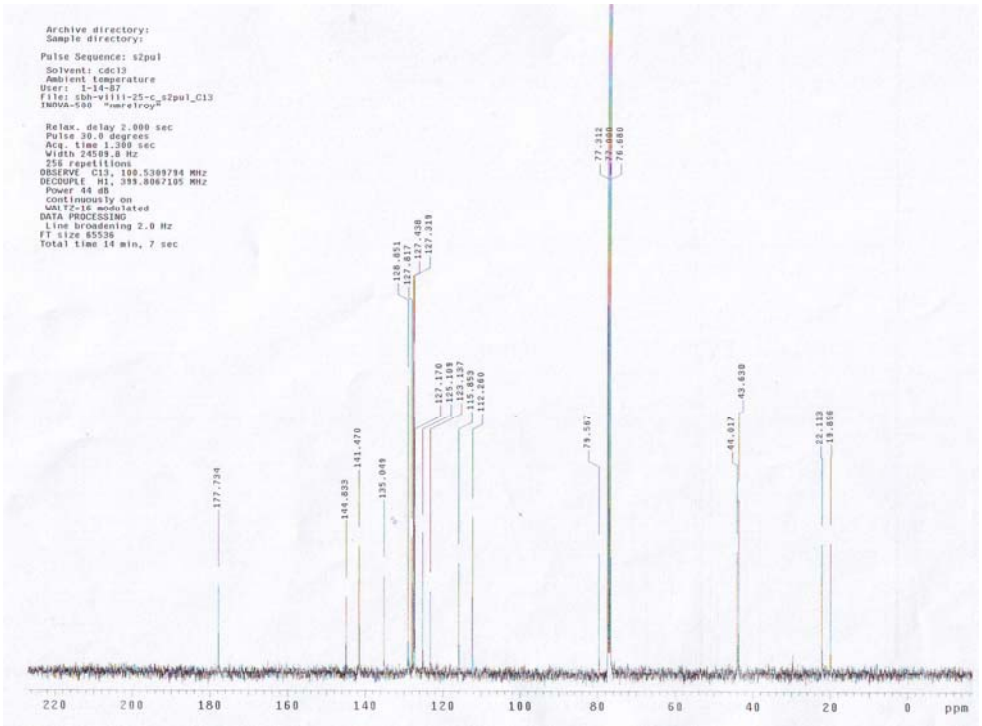
3.21f

TLC (SiO_2): R_f = 0.30 (toluene:ethyl acetate, 30:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.13 (m, 7H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.12 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 5.12 (d, *J* = 17.6 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.57 (d, *J* = 15.6 Hz, 1H), 2.97 (s, 1H), 1.16 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 144.8, 141.5, 135.0, 128.9, 127.8, 127.4, 127.3, 127.2, 125.1, 123.1, 115.9, 112.3, 79.6, 44.0, 43.6, 22.1, 19.9. HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{major} = 12.8 min, t_{minor} = 17.1 min; ee = 93%., $[\alpha]_D^{26}$ +96.6 (c 1.24, $CHCl_3$). FTIR (neat): υ 3431, 2923, 2359, 1709, 1601, 1485, 1455, 1429, 1340, 1169, 1120, 1063, 1030, 959, 920, 859, 843, 816, 734, 712, 698 cm^{-1}. HRMS (CI) Calcd. for $C_{20}H_{21}NO_2Br(M+H)^+$: 386.0756 Found: 386.0758.

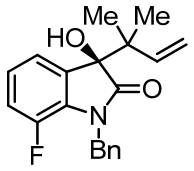
^{1}H NMR



^{13}C NMR



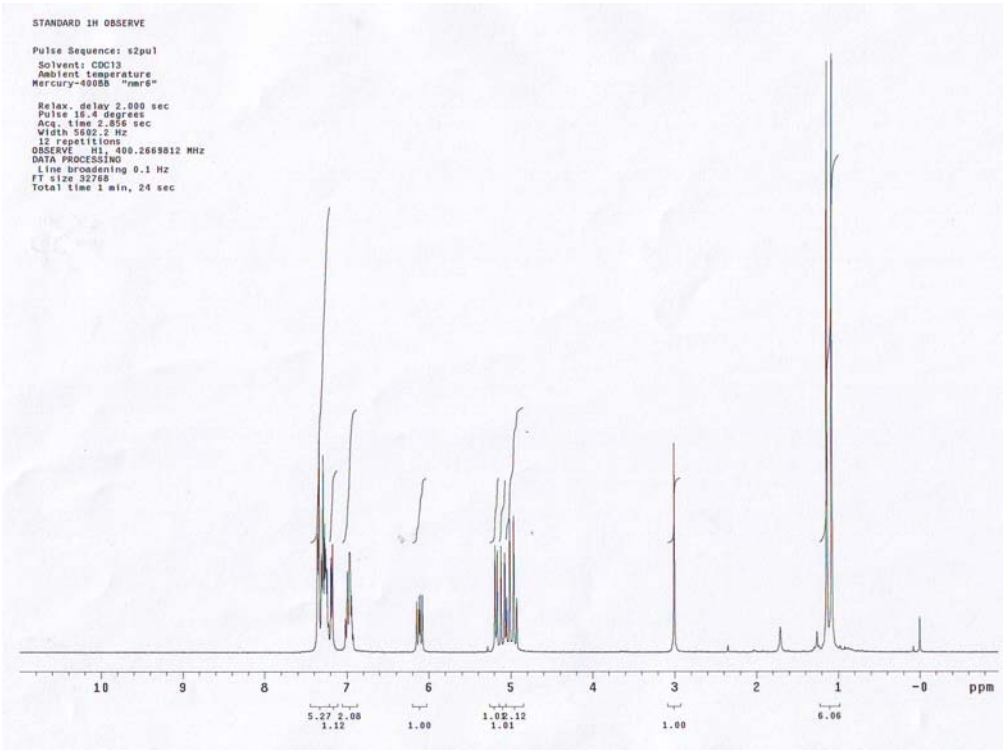
(*R*)-1-benzyl-7-fluoro-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one



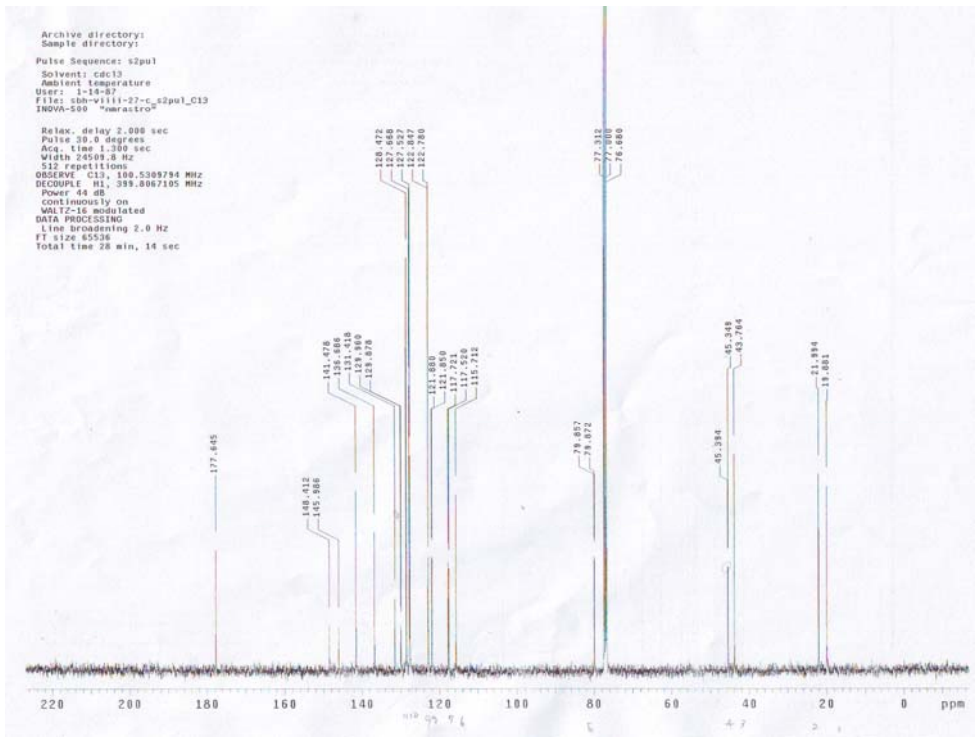
3.21g

TLC (SiO_2): R_f = 0.25 (toluene:ethyl acetate, 30:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.18 (m, 6H), 7.02-6.92 (m, 2H), 6.11 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 5.03 (d, *J* = 15.2 Hz, 1H), 4.95 (d, *J* = 15.2 Hz, 1H), 3.00 (s, 1H), 1.14 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 147.2 (d, J_{C-F}= 243.8 Hz), 141.5, 136.7, 131.4, 129.0 (d, J_{C-F}= 8.2 Hz), 128.5, 127.7, 127.5, 122.8 (d, J_{C-F}= 6.7 Hz), 121.9 (d, J_{C-F}= 3.0 Hz), 117.7 (d, J_{C-F}= 20.2 Hz), 115.7, 79.9 (d, J_{C-F}= 1.5 Hz), 45.4 (d, J_{C-F}= 4.5 Hz), 43.8, 22.0, 19.9. HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{major} = 11.3 min, t_{minor} = 16.2 min; ee = 94%., $[\alpha]_D^{26}$ +99.6 (c 0.78, $CHCl_3$). FTIR (neat): υ 3407, 2924, 1697, 1626, 1488, 1470, 1455, 1382, 1361, 1247, 1197, 1162, 1133, 1028, 1005, 949, 924, 915, 867, 817, 779, 738, 710, 694 cm^{-1}. HRMS (CI) Calcd. for $C_{20}H_{21}NO_2F$ $(M+H)^+$: 326.1556 Found: 326.1554. mp (DCM/Hexane) 119-120 ^oC, White solid

^{1}H NMR



^{13}C NMR



Chapter 4: Total Synthesis of (+)-Roxaticin *via* C-C Bond Forming TransferHydrogenation

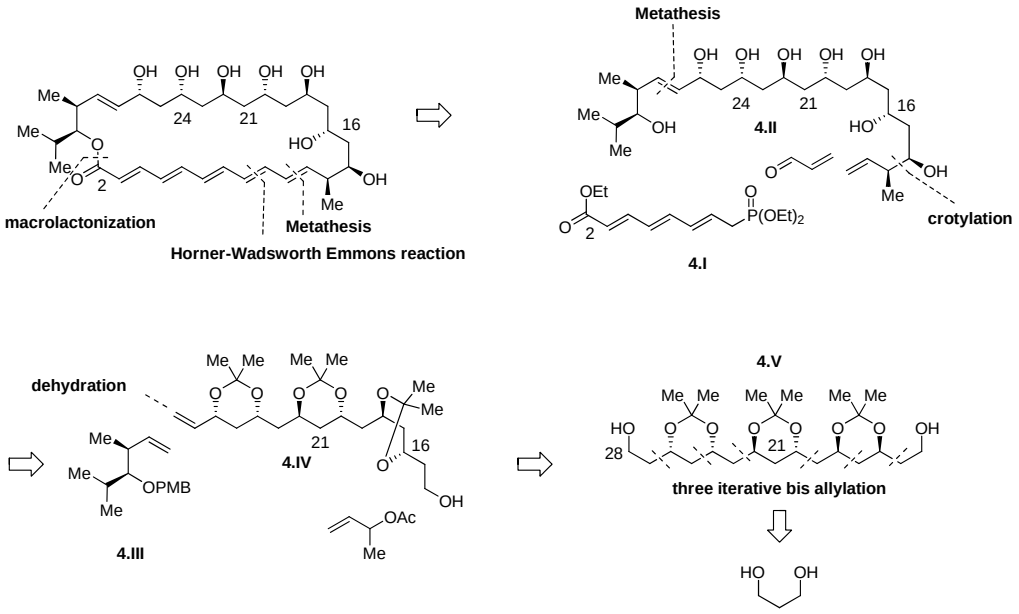
4.1 INTRODUCTION

Polyketide natural products represent a broad class of secondary metabolites that are used extensively in medicine.[1,2] Many top selling small molecules are polyketides[2,3] and it is estimated that polyketides are five times more likely to possess drug activity than the other natural product families.[3] As investigations in polyketide biosynthesis[4] and chemical biology continue to uncover important biochemical pathways and novel therapeutic targets, the design of synthetic[5] and bioengineered[6] methods for polyketide construction remains at the forefront of current research. The complex issues of stereoselectivity posed by polyketides are most often addressed through the use of chiral auxiliaries, chiral reagents, and premetalated nucleophiles.[5] Although these methods are highly effective, they often require multistage preactivation and excessive byproduct generation. By utilizing the recently developed asymmetric C-C bond forming transfer hydrogenation[7], the total synthesis of (+)-roxaticin[8,9,10] was achieved.

4.2 SYNTHETIC PLAN

This approach takes the advantage of carbonyl allylation[7f,11a-d] and crotylation[7f,11e] protocols recently developed in our laboratory, wherein primary alcohol dehydrogenation concurrently triggers aldehyde formation and reductive generation of allyliridium nucleophiles, enabling asymmetric carbonyl allylation and crotylation directly from the alcohol oxidation level. The synthetic plan is presented in Scheme 4.1. The macrocyclic

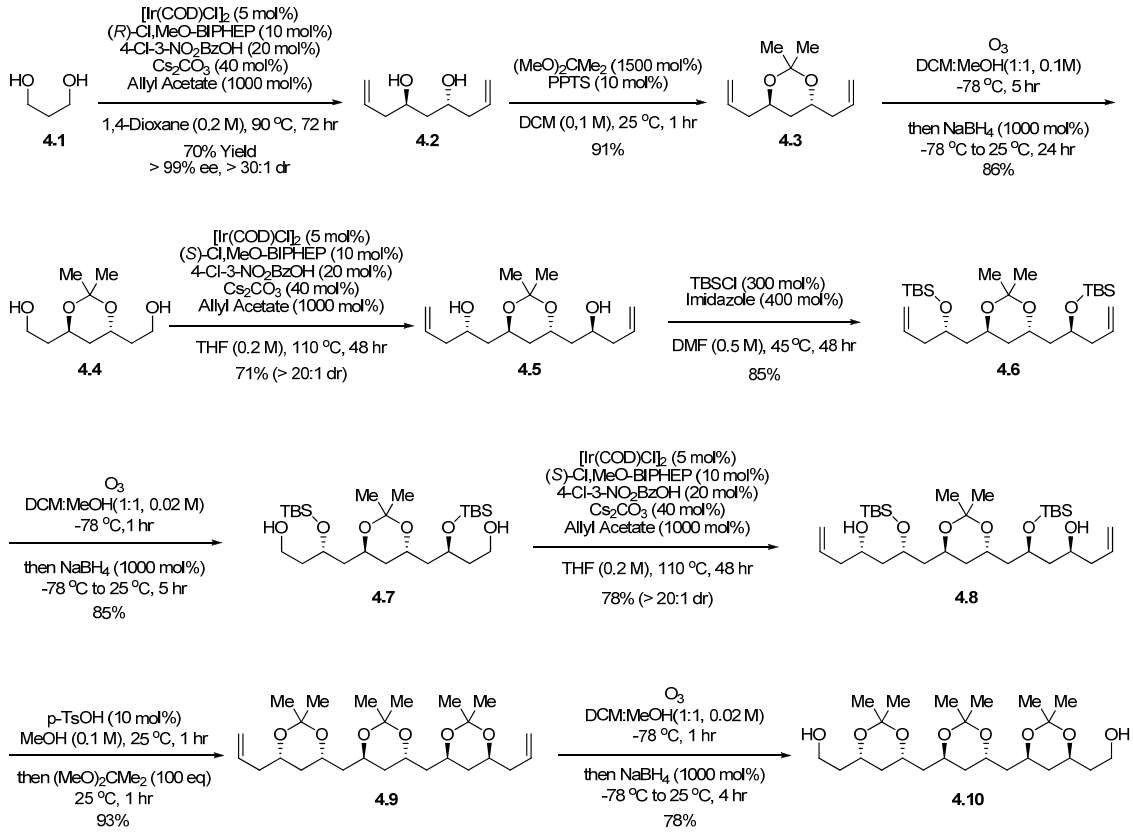
ring was formed according to the Yamaguchi method.[12] Installation of the oxopentaene fragment exploited a sequence involving cross metathesis-Horner-Wadsworth-Emmons[13] olefination, which led to fragments **4.I** and **4.II**. Internal olefin of **4.II** was prepared using cross metathesis reaction. Elaboration of the protected 1,3-polyol **4.V** to (+)-roxaticin required differential elongation of the homotopic diol termini, which was achieved *via* sequential dehydration-cross-metathesis at C28 and direct carbonyl crotylation from the alcohol oxidation level at C14. Iterative two-directional carbonyl allylation of 1,3-diols[11c,d,14] was envisioned to deliver the requisite C_2-symmetric 1,3-polyol substructure **4.V**.



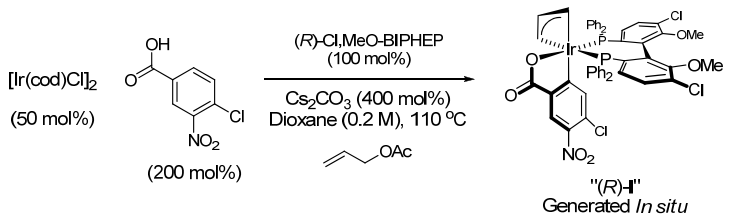
Scheme 4.1 Retrosynthetic analysis of (+)-roxaticin.

4.3 SYNTHESIS OF POLYOL FRAGMENT 4.IV

Two directional bis *C*-allylation[11c,d] was conducted with 1,3-propanediol **4.1** (Scheme 4.2). With the *ortho*-cyclometalated iridium *C,O*-benzoate **(*R*)-I** generated *in situ* from $[Ir(cod)Cl]_2$, (*R*)-Cl,MeO-BIPHEP, 4-chloro-3- nitrobenzoic acid, and allyl acetate (Scheme 4.3), double allylation product **4.2** was isolated in 70% yield and >99% ee. The minor enantiomer of the monoadduct was converted to the *meso*-diastereomer of **4.2**.[15,16] Interestingly, in the course of a synthetic approach to (+)-phorboxazole A,[17]



Scheme 4.2 Synthesis of polyol fragment **4.IV**.



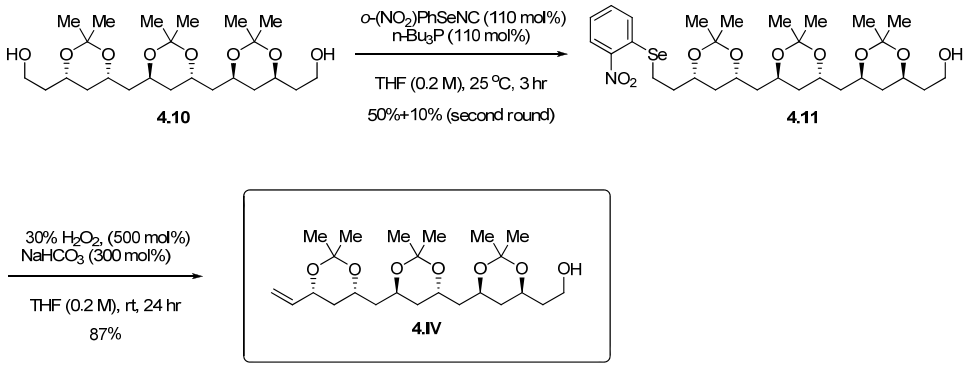
Scheme 4.3 *Ortho*-cyclometalated iridium *C,O*-benzoate **(*R*)-I** generated *in situ*.

the *mono*-TBS (*tert*-butyldimethylsilyl) derivative of C_2-symmetric diol (*S,S*)-**4.2** was prepared in seven steps from propylene glycol through successive use of Brown's reagent for asymmetric carbonyl allylation, $Ipc_2(n\text{-}C_3H_5)B$, and an improved procedure delivers (*S,S*)-**4.2** in four steps from acetylacetone. On a larger scale (20 mmol), to mitigate cost, double allylation reactions were conducted using the corresponding (*R*)-BINAP complex, which provided **4.2** in 51% yield with equivalent levels of absolute stereocontrol.

Conversion of **4.2** to acetonide **4.3** followed by ozonolysis of the olefinic termini provides the homologous diol **4.4**, constituting "one iteration" of two-directional carbonyl allylation from the alcohol oxidation level. In principle, subsequent iterations of two-directional carbonyl allylation could be performed from the diol or dialdehyde oxidation level. However, the *β*-alkoxy aldehydes were found to be quite unstable, whereas diol intermediates, such as **4.4**, were highly tractable and could be stored for long periods of time under ambient conditions without decomposition. Therefore, in subsequent iterations of two-directional carbonyl allylation, ozonolysis reactions were quenched with $NaBH_4$ to furnish the homologous diols. In large scale ozonolysis reactions, $NaBH_4$ reduction of the ozonide is preferred as this protocol circumvents generation of

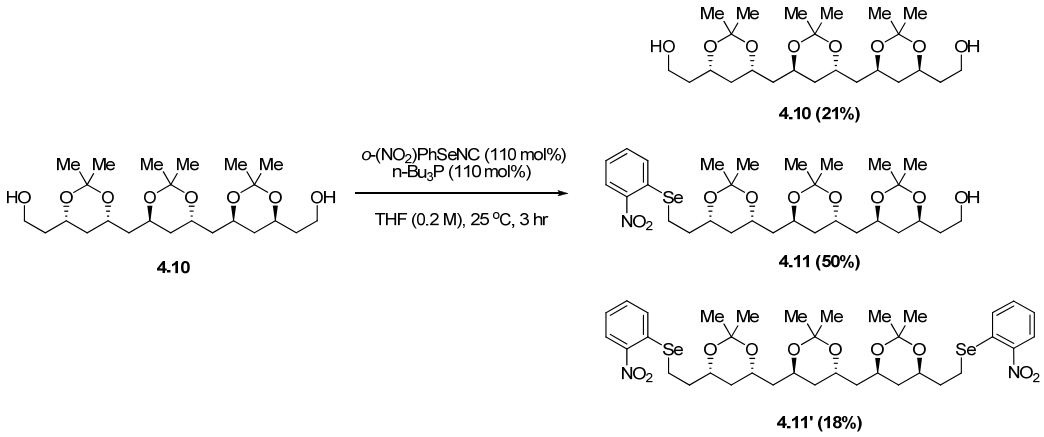
stoichiometric organic byproducts; hence, facilitates product purification.[18] Subsequent iteration of two-directional carbonyl allylation of **4.4** was conducted. Double allylation product **4.5** was produced in 71% yield and >20:1 dr, this reaction required shorter reaction time (48 hr) than the first double allylation. Protection with TBS group (**4.6**) followed by ozonolysis generated diol **4.7**, which was ready for the third carbonyl bis-allylation reaction. The final bis allylation produced bis-homoallylic alcohol **4.8** in 78% and >20:1 dr. Protecting group swap (**4.9**) followed by ozonolysis gave three acetonide protected diol **4.10**. With three iterations of two-directional allylation, complete levels of catalyst-directed diastereoselectivity were observed, providing rapid access to the acetonide-protected C_2-symmetric 1,3-polyol **4.10** as a single diastereomer. Thus, *tris*-acetonide **4.10**, which possesses six stereocenters, was prepared in only nine steps from 1,3-propanediol (Scheme 4.2).

Differentiation of diol temini of *tris*-acetonide **4.10** was required. As described in Scheme 4.4, Grieco's two-step method for primary alcohol dehydration was conducted.[19]



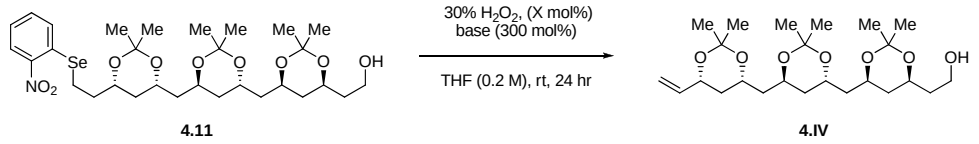
Scheme 4.4 Differential elongation of diol temini of **4.10**.

Because the diol termini of **4.10** are homotopic, the selenylation product appeared as a component of a statistical mixture with 1.1 eq of *o*-(NO_2)PhSeCN. Mono-selenide **4.11** was obtained in 50% yield along with the formation of diselenide **4.11'** in 18% yield (Scheme 4.5). Recovered starting material **4.10** (21%) was submitted to the second round of the reaction. The combined yield of the two reactions was 60%.



Scheme 4.5 Selenylation reaction of **4.10** with *o*-(NO_2)PhSeCN.

The second elimination step was very sensitive to base and the amount of H_2O_2. Among all the bases attempted, $NaHCO_3$ appeared to be the best base additive (Table 4.1, entry 6). Reducing the amount of H_2O_2 from 1000 mol% to 500 mol% afforded the desired product **4.VI** in 87% yield (Table 4.1, entry 7).



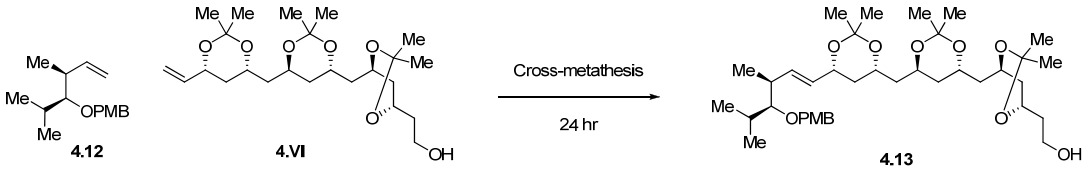
4.11 **4.IV**

entry	amount of H_2O_2	base (300 mol%)	yield of **4.VI**
1	1000 mol%	pyridine	trace
2	1000 mol%	TEA	trace
3	1000 mol%	KOAc	trace
4	1000 mol%	K_2CO_3	12%
5	1000 mol%	Na_2CO_3	trace
6	1000 mol%	$NaHCO_3$	34%
7	**500 mol%**	**$NaHCO_3$**	**87%**

Tabel 4.1 Optimization of the elimination reaction of **4.11**.

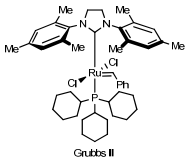
4.4 SYNTHESIS OF FRAGMENT 4.II

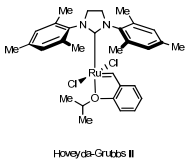
Cross metathesis was attempted with the previously prepared homoallylic ether



4.12 **4.VI** **4.13**

entry	catalyst	amount	solvent	temperatrue	yield
1	Grubbs II	5 mol%	Toluene	90 °C	21%
2	Grubbs II	5 mol%	DCE	90 °C	19%
3	Grubbs II	5 mol%	DCM	40 °C	23%
4	Hoveyda-Grubbs II	5 mol%	Toluene	90 °C	23%
5	Hoveyda-Grubbs II	5 mol%	DCE	90 °C	24%
6	Hoveyda-Grubbs II	5 mol%	DCM	40 °C	36%
7	**Hoveyda-Grubbs II**	**10 mol%**	**DCM**	**40 °C**	**53%**

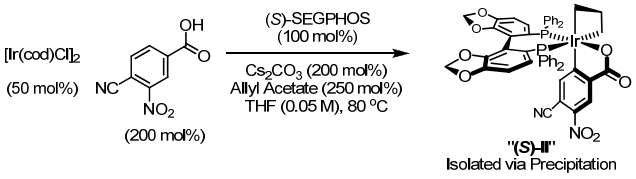




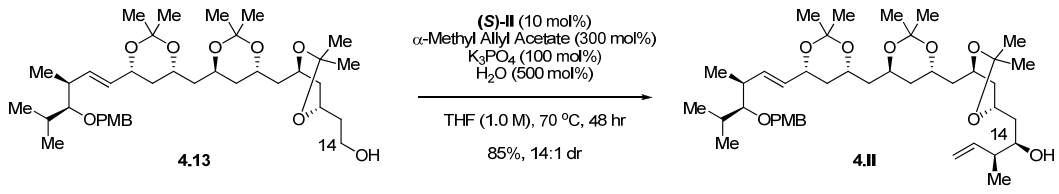
Tabel 4.2 Optimization of cross metathesis of **4.VI**.

4.12[20] with various catalytic systems (Table 4.2). Hoveyda-Grubbs II catalyst was more reactive than Grubbs II catalyst in most cases. At high reaction temperature, **4.13** was produced in low yield because homo-dimerization dominated (Table 4.2, entry 1, 2, 4 and 5). With 10 mol% of Hoveyda-Grubbs II catalyst, 53% of cross coupling product **4.13** was obtained in DCM at 40 ^{o}C (Table 4.2, entry 7).

Direct carbonyl crotylation from the alcohol oxidation level at C14 using the preformed iridium *C,O*-benzoate complex (*S*)-**II** (Scheme 4.6) delivered the desired adduct **4.II** in 85% yield with 14:1 *anti*-diastereoselectivity (Scheme 4.7). Crotylation with Ir catalyst[11e] generated *in situ* showed lower selectivity (7:1) and required higher reaction temperature (90 ^{o}C). In most of the conventional carbonyl crotylation methods, the alcohol has to be oxidized to aldehyde for the reaction. However, the Ir catalytic system avoided the oxidation state manipulation and reduced the number of reaction steps.



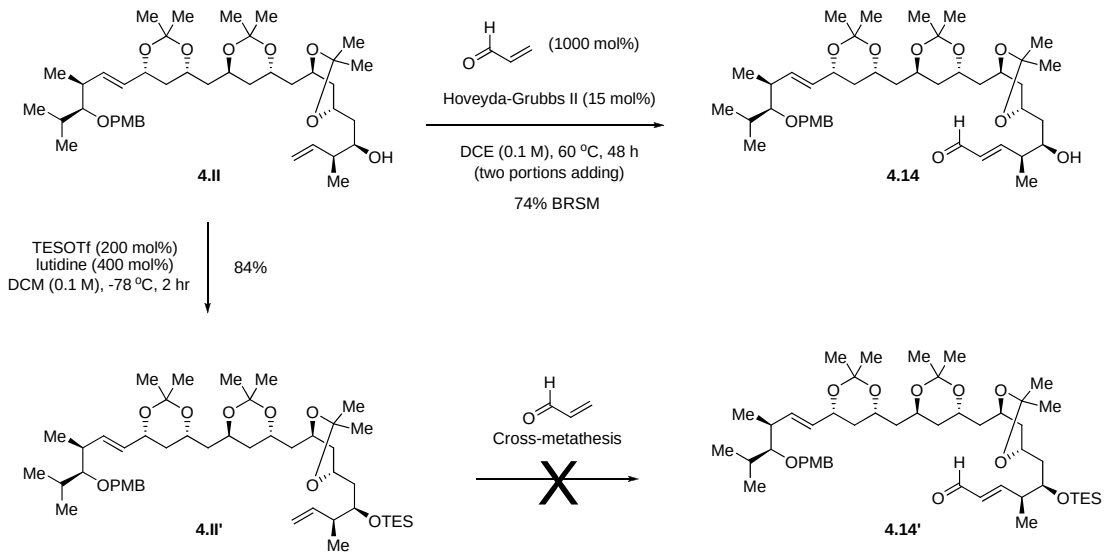
Scheme 4.6 *Ortho*-cyclometalated iridium *C,O*-benzoate **(*S*)-II** isolated by precipitation.



Scheme 4.7 Direct carbonyl crotylation from the alcohol oxidation level.

4.5 ENDGAME OF (+)-ROXATICIN

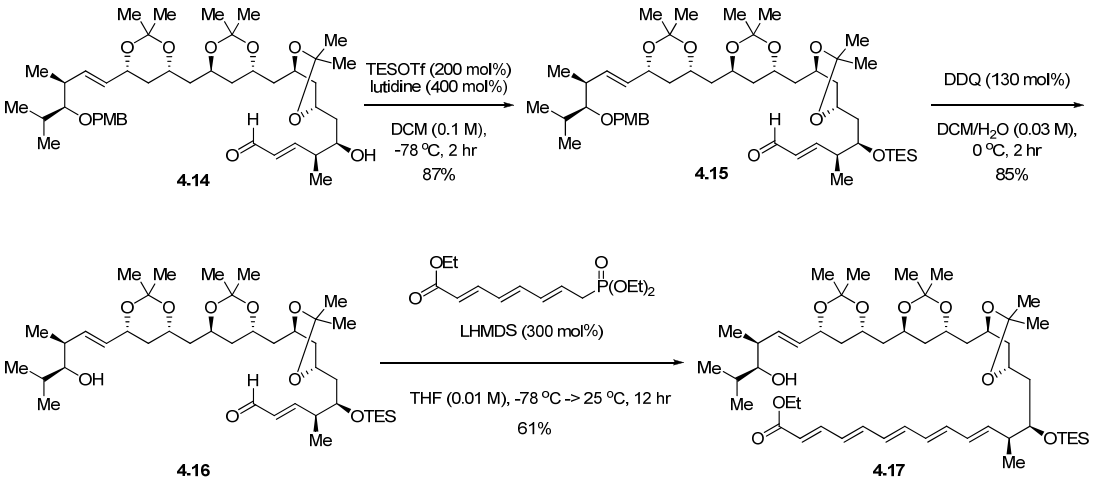
With homoallylic alcohol **4.II** in hand, installation of the polyene substructure was undertaken. The unprotected homoallylic alcohol **4.II** was subjected to cross-metathesis with acrolein to deliver the corresponding enal **4.14** in 74% yield (BRSM) with complete (*E*)-selectivity as determined by ^{1}H NMR (Scheme 4.8).[21] TES protected ether **4.II'** did not participate in cross-metathesis, presumably due to the sterically demanding environment at the homoallylic olefin.



Scheme 4.8 Cross-metathesis of **4.II** with acrolein.

Subsequent protection of the C14 alcohol provide the triethylsilyl (TES) ether **4.15**, which was followed by oxidative removal of the *para*-methoxybenzyl ether to

furnish hydroxy enal **4.16** (Scheme 4.9). Exposure of **4.16** to the previously reported Horner-Wadsworth-Emmons reagent, $EtO_2C(CH{=}CH)_3CH_2PO(OEt)_2$[22] delivered

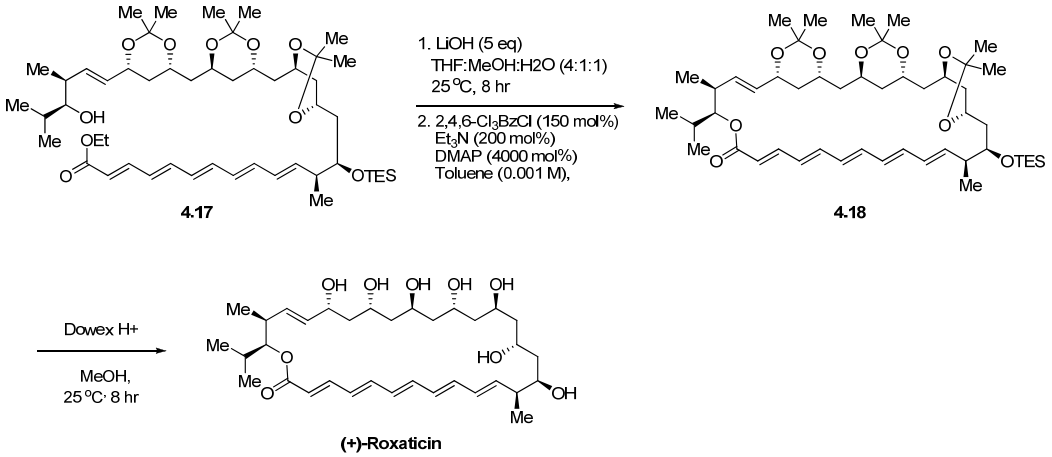


Scheme 4.9 Synthesis of polyunsaturated ester **4.16**.

polyunsaturated ester **4.17** in 61% yield. This transformation, which involved LHMDS mediated lithium enolate generation, represented the use of a premetalated *C*-nucleophile in the longest linear sequence.

Ester hydrolysis followed by Yamaguchi lactonization21[23] (**4.18**) and global deprotection, as practiced in prior syntheses by Mori[9c-d] and Evans,[9e] were attempted to deliver (+)-roxaticin (Table 4.3). Yamaguchi lactonization was very sensitive to the reaction temperature and time. High reaction temperature only gave a trace amount of product (Table 4.3, entry 1 and 2). Finally, 15% yield of roxaticin was obtained at 50 °C for 8 hr (Table 4.3, entry 3). Prolonging the reaction time improved product yield (Table 4.3, entry 4). However, further increase of the reaction time decreased product yield,

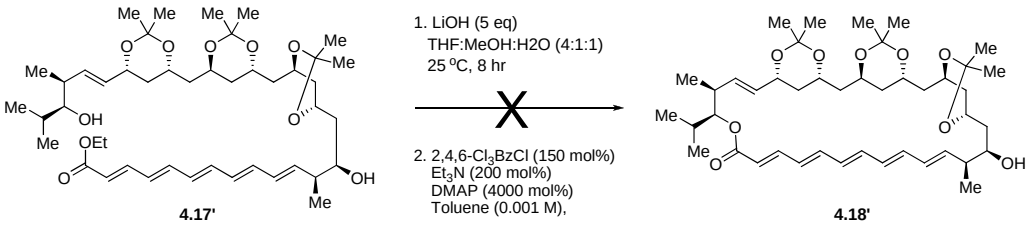
presumably due to the instability of the product (Table 4.3, entry 5). This three-step sequence delivered (+)-roxaticin in 31% yield. Additionally, attempted



entry	T of latonization	reaction time	yield of roxaticin
1	110 °C	8 hr	trace
2	80 °C	8 hr	trace
3	50 °C	8 hr	15%
4	**50 °C**	**12 hr**	**31%**
5	50 °C	24 hr	18%
6	25 °C	8 hr	trace

Table 4.3 Optimization of macrolatonization.

macrolactonization of **4.16'**, which lacks a C14 hydroxyl protecting group, was unsuccessful under various reaction conditions (Scheme 4.10).



Scheme 4.10 Attempted macrolactonization of **4.17'**.

4.6 SUMMARY

In summary, in this novel application of "*C-C bond forming hydrogenation*" methodology, (+)-roxaticin was prepared from 1,3-propane diol over 20 steps (longest linear sequence), with a total number of 29 manipulations. Notably, 9 of 10 C-C bonds formed in the longest linear sequence were made *via* metal catalysis (7 hydrogen-mediated C-C couplings, 2 cross-metatheses) in processes that exploit "native functionality" (alcohols, olefins). This approach circumvents additional manipulations associated with the use of non-native functional groups or substructures to mediate bond construction, as evident in the use of chiral auxiliaries; it also minimized (re)functionalizations, especially redox manipulations. Indeed, as demonstrated in carbonyl additions from the alcohol oxidation level, as in the conversion of **4.13** to **4.II**, the union of oxidation-construction events allows one to bypass discrete alcohol oxidation while gaining access to more tractable synthetic intermediates in the form of alcohols. These features are aligned with longstanding ideals of synthetic efficiency.[24,25]

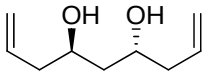
4.7 EXPERIMENTAL SECTION

General

All reactions were run under an atmosphere of nitrogen. Tetrahydrofuran, toluene, dichloromethane were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Commercially available allyl acetate (Acros) and α-methyl allyl acetate (acetic acid 3-buten-2-yl ester, TCI) were purified by distillation prior to use. $[Ir(cod)_2Cl]$ was used as received from Strem Chemicals. Cesium carbonate were purchased from Alfa Aesar and used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M or M-1) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in hertz (Hz).

Experimental Details

(4*R*,6*R*)-Nona-1,8-diene-4,6-diol



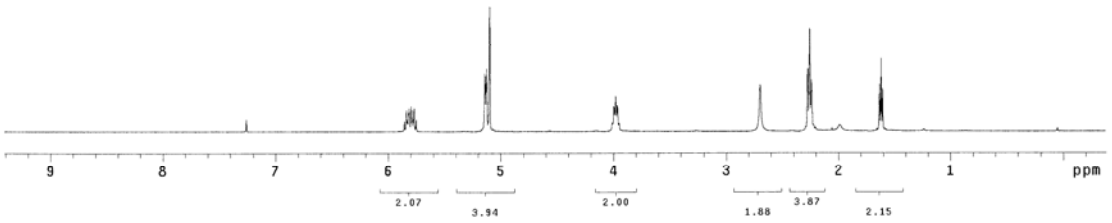
4.2

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (1.35 g, 2.012 mmol, 5 mol%), (*R*)-Cl,MeO-BIPHEP (2.61 g, 4.008 mmol, 10 mol%), Cs_2CO_3 (5.22 g, 16.03 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (1.62 g, 8.016 mmol, 20 mol%) was added 1,4-dioxane (100 mL) followed by allyl acetate (43 mL, 0.401 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. 1,3-Propanediol (3.05 g, 40.08 mmol, 100 mol%) in 1,4-dioxane (100 mL, 0.4 M) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 72 hr. The reaction mixture was filtered through the pad of celite and evaporated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 to 1:1 with 0.1% TEA) provided **4.2** (4.36 g, 27.93 mmol, dr > 30:1) as pale yellow oil in 70% yield.

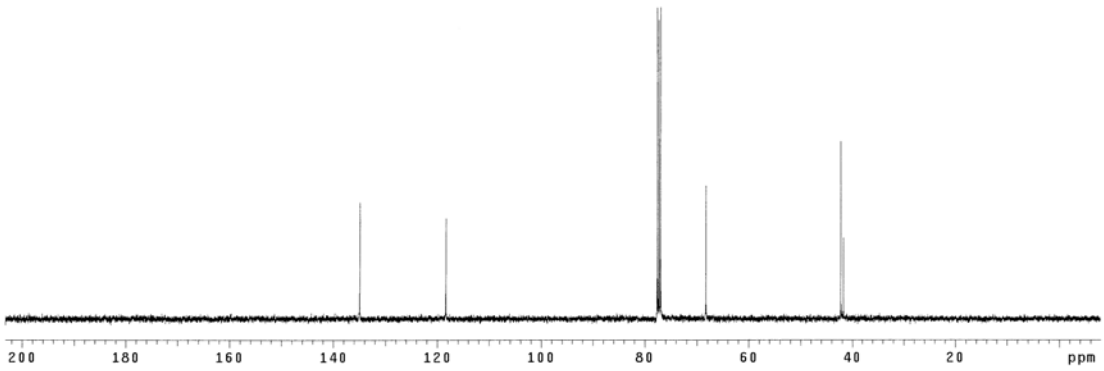
TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:2). $[\alpha]_D^{24}$ = –23.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.75 (m, 2H), 5.15-5.09 (m, 4H), 4.01-3.94 (m, 2H), 2.69 (br s, 2H), 2.28-2.23 (m, 4H), 1.62 (t, *J* = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 118.3, 68.3, 42.2, 41.7. FTIR (neat): υ 3346, 3076, 3005, 2978, 2936, 1827, 1641, 1433, 1335, 1230, 1131, 1071, 1046, 994, 871, 830 cm^{-1}. HRMS (CI) Calcd. for $C_9H_{17}O_2$ $(M+H)^+$: 157.1229, Found: 157.1225. HPLC: Enantiomeric excess was

determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 17.2 min, t_{major} = 40.8 min; ee > 99%.

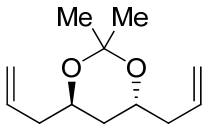
^{1}H NMR



^{13}C NMR



(4*R*,6*R*)-4,6-Diallyl-2,2-dimethyl-1,3-dioxane

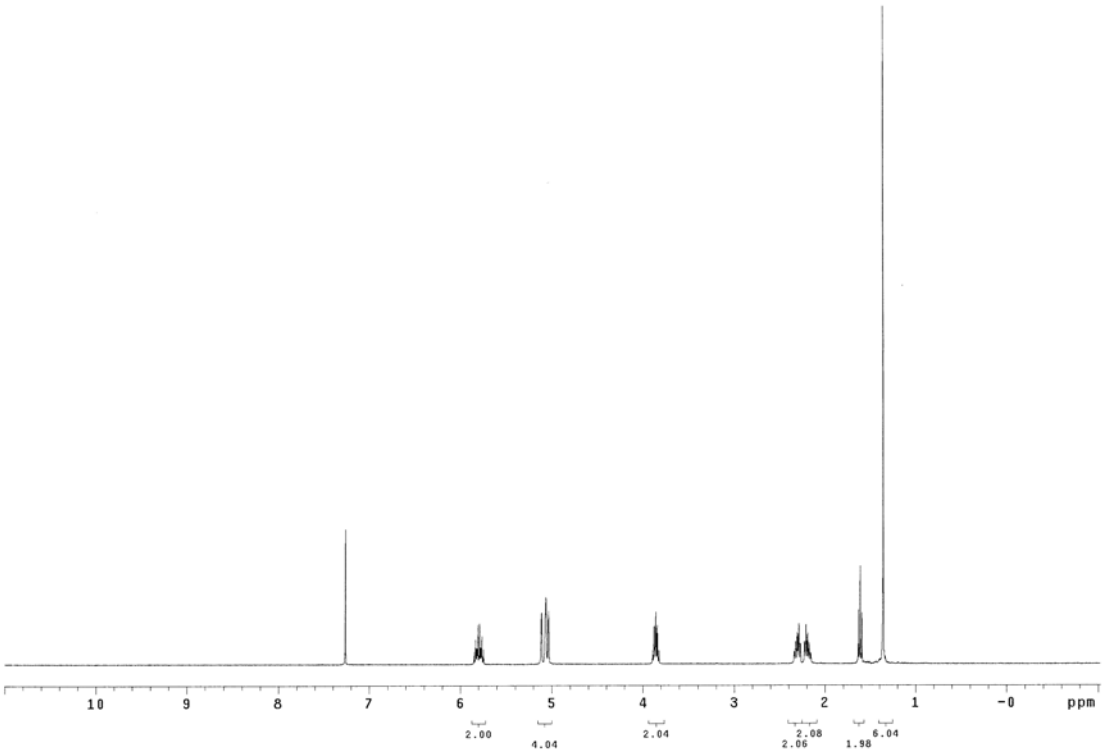


4.3

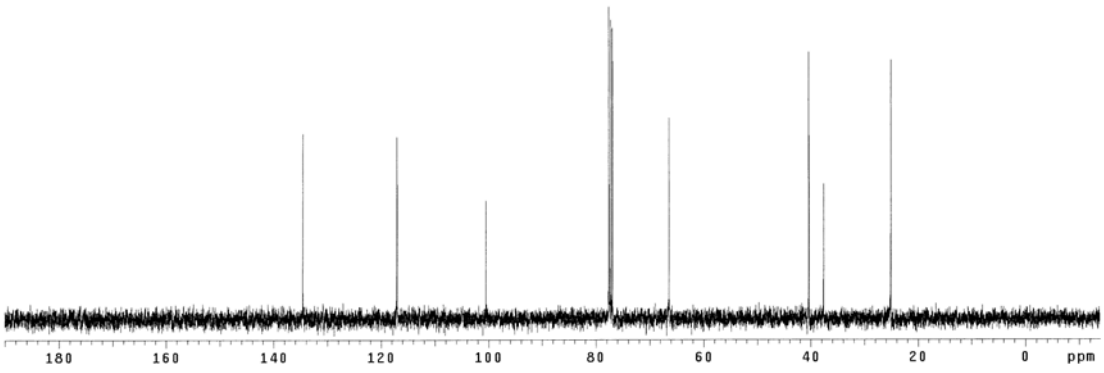
To a stirred solution of the diol **4.2** (3.5 g, 22.42 mmol, 100 mol%) in DCM (224 mL, 0.1 M) were added 2,2-dimethoxypropane (41 mL, 0.336 mol, 1500 mol%) and pyridinium *p*-toluenesulfonate (0.56 g, 2.242 mmol, 10 mol%) at ambient temperature. The reaction mixture was stirred for 1 hr and quenched with saturated aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (100 mL × 2). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:15 with 0.1% TEA) to give the acetonide **4.3** (3.99 g, 20.33 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:20). $[\alpha]_D^{24}$ = –56.0 (*c* = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 5.84-5.73 (m, 2H), 5.10-5.01 (m, 4H), 3.88-3.80 (m, 2H), 2.33-2.25 (m, 2H), 2.21-2.13 (m, 2H), 1.59 (t, *J* = 7.6 Hz, 2H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 117.1, 100.5, 66.4, 40.4, 37.7, 25.1. FTIR (neat): υ 3077, 2986, 2937, 1831, 1642, 1431, 1377, 1361, 1172, 1121, 1015, 993, 911, 833, 814 cm^{-1}. HRMS (CI) Calcd. for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1542, Found: 197.1540.

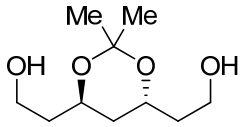
^{1}H NMR



^{13}C NMR



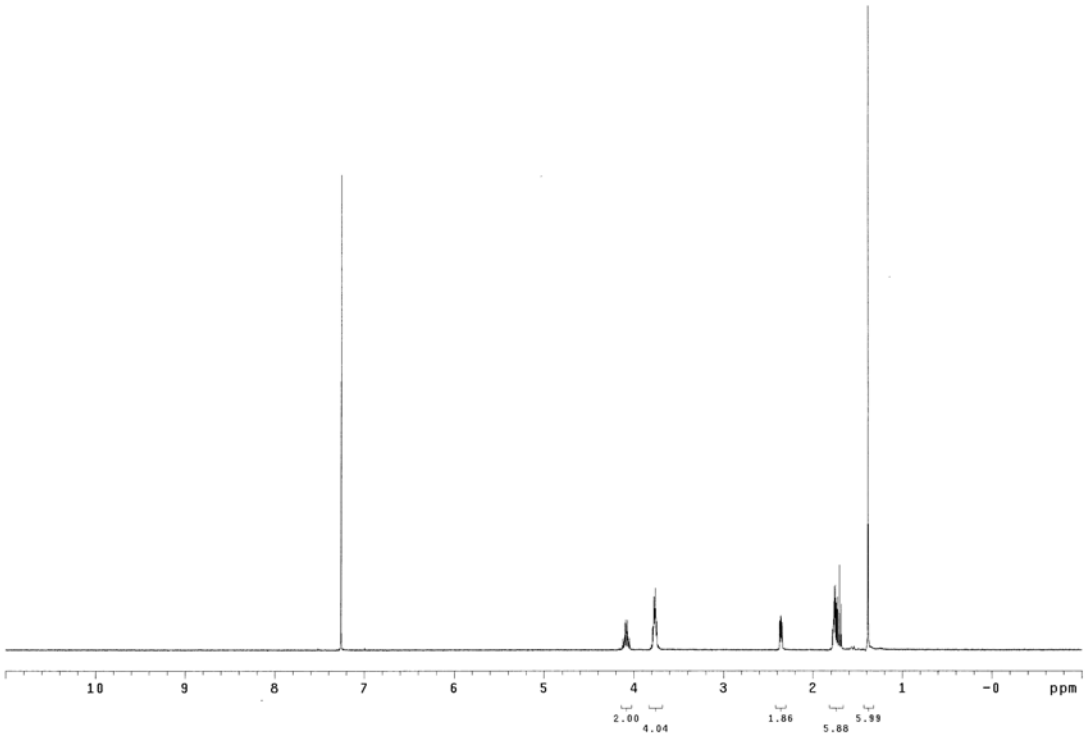
2,2'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)diethanol



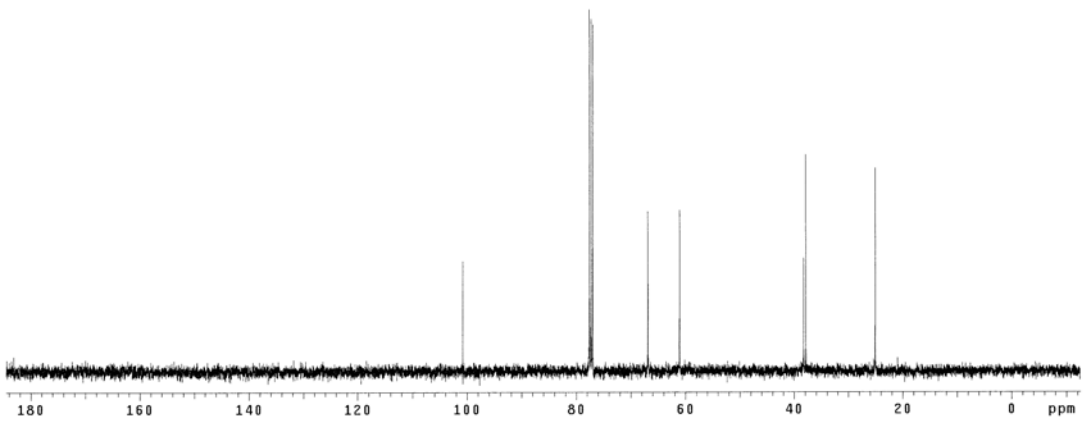
4.4

To a stirred solution of the acetonide **4.3** (3.8 g, 19.36 mmol, 100 mol%) in DCM/MeOH (1:1, 130 mL, 0.15 M) was bubbled ozone at −78 ^{o}C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (7.3 g, 0.194 mol, 1000 mol%) was added in one portion at – 78 ^{o}C and the resulting solution was slowly warmed to ambient temperature. The mixture was stirred for 24 hr at ambient temperature, and then quenched with H_2O (40 mL). The resulting mixture was concentrated and extracted with DCM (200 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 to ethyl acetate:methanol, 20:1 with 0.1% TEA) to give the diol **4.4** (3.42 g, 16.74 mmol) as a colorless oil in 86% yield. TLC (SiO_2): R_f = 0.28 (ethyl acetate). $[\alpha]_D^{25}$ = –29.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08-4.00 (m, 2H), 3.71 (m, 4H), 2.62 (s, 2H), 1.75-1.69 (m, 4H), 1.66 (t, *J* = 7.6 Hz, 2H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.8, 66.8, 61.1, 38.3, 37.9, 25.1. FTIR (neat): υ 3357, 2986, 2939, 2879, 2359, 1654, 1441, 1416, 1381, 1223, 1164, 1123, 1014, 974, 937, 902, 877 cm^{-1}. HRMS (CI) Calcd. for $C_{10}H_{21}O_4$ $[M+H]^+$: 205.1440, Found: 205.1438.

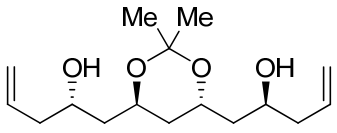
^{1}H NMR



^{13}C NMR



(2*S*,2'*S*)-1,1'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)dipent-4-en-2-ol

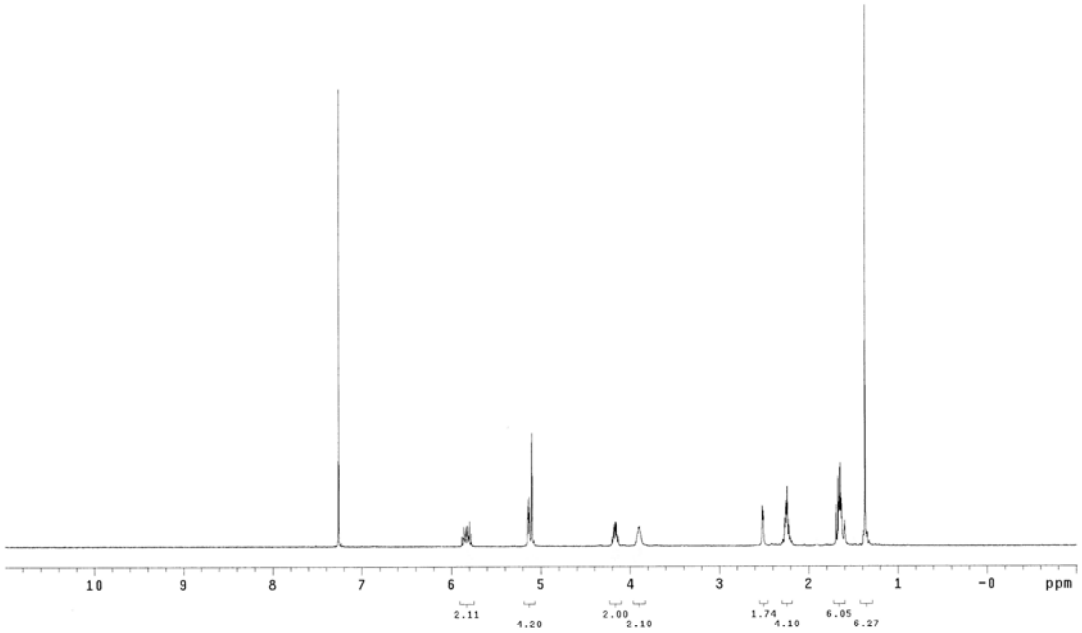


4.5

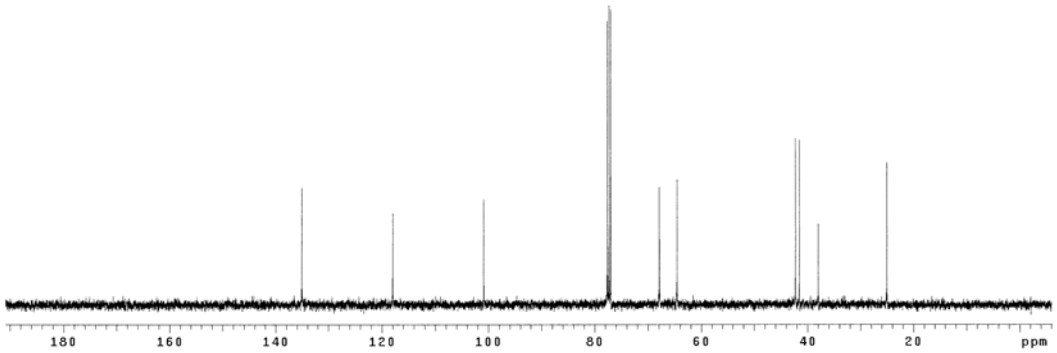
To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (0.58 g, 0.857 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (1.12 g, 1.714 mmol, 10 mol%), Cs_2CO_3 (2.23 g, 6.856 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (0.69 g, 3.428 mmol, 20 mol%) was added THF (43 mL) followed by allyl acetate (1.85 mL, 0.171 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. The diol **4.4** (3.5 g, 17.14 mmol, 100 mol%) in THF (43 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 110 ^{o}C for 48 hr. The reaction mixture was filtered through the pad of celite and evaporated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 to 1:1 with 0.1% TEA) provided **4.5** (3.46 g, 12.17 mmol, dr > 20:1) as pale yellow oil in 71% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{24}$ = –18.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.74 (m, 2H), 5.11-5.06 (m, 4H), 4.17-4.09 (m, 2H), 3.86 (br m, 2H), 2.61 (br s, 2H), 2.25-2.15 (m, 4H), 1.66-1.55 (m, 6H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 118.0, 100.9, 67.9, 64.6, 42.3, 41.5, 38.0, 25.0. FTIR (neat): υ 3415, 3075, 2985, 2938, 2917, 2850, 1837, 1717, 1640, 1433, 1380, 1222, 1163, 1129, 1081, 1035, 994, 869, 810 cm^{-1}. HRMS (CI) Calcd. for $C_{16}H_{29}O_4$ $(M+H)^+$: 285.2066, Found: 285.2066.

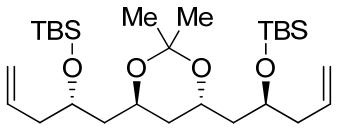
^{1}H NMR



^{13}C NMR



(2*S*,2'*S*)-1,1'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(pent-4-ene-2,1 diyl)bis(oxy)bis(*tert*-butyldimethylsilane)

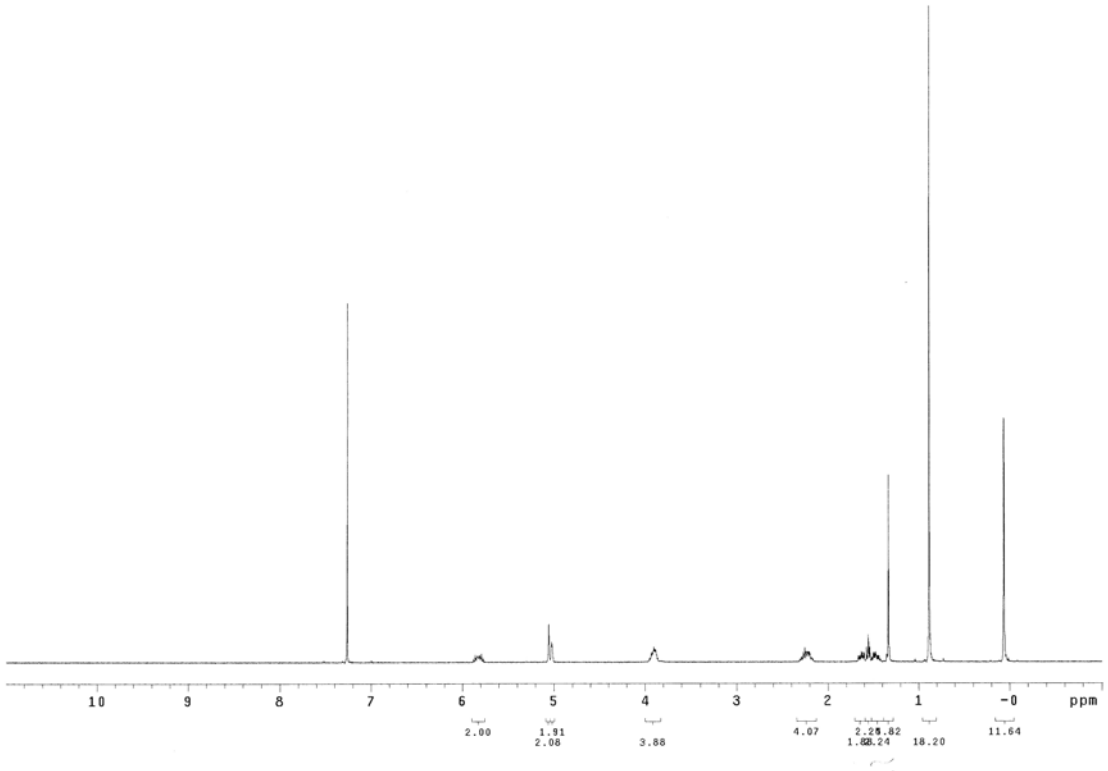


4.6

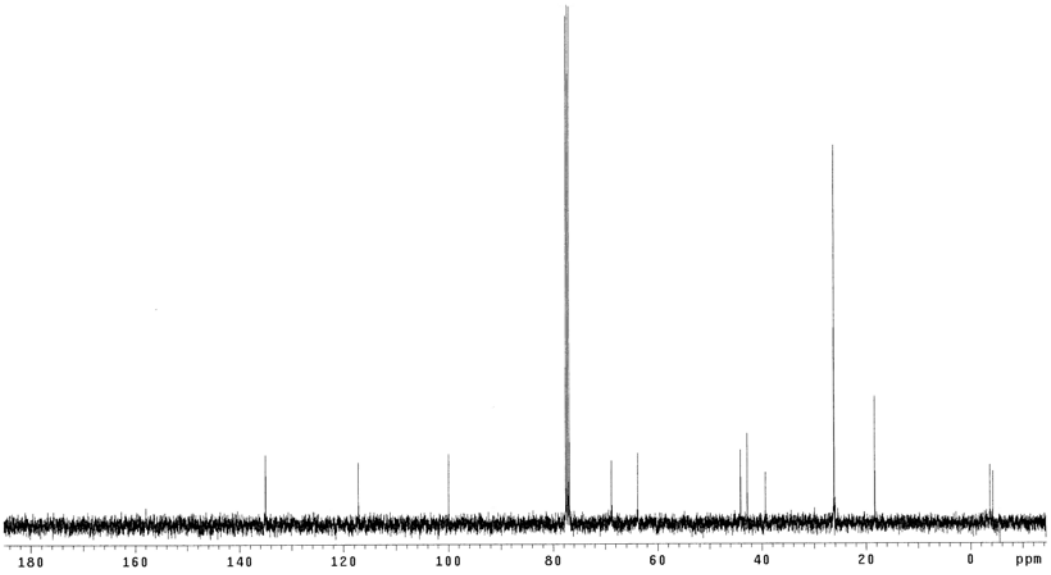
To a stirred solution of the diol **4.5** (0.49 g, 1.723 mmol, 100 mol%) in DMF (3.4 mL, 0.5 M) were added imidazole (0.47 g, 6.892 mmol, 400 mol%) and TBSCl (0.78 g, 5.169 mmol, 300 mol%) at ambient temperature. The reaction mixture was allowed to stir for 48 hr at 45 ^{o}C, and then quenched with H_2O (5 mL). The reaction mixture was extracted with EtOAc (15 mL × 2). The combined organic extracts were washed with H_2O (3 mL × 2), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:30 with 0.1% TEA) to give **4.6** (0.75 g, 1.464 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes, 1:30). $[\alpha]_D^{26}$ = +24.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.77 (m, 2H), 5.11-5.01 (m, 4H), 3.95-3.82 (m, 4H), 2.30-2.16 (m, 4H), 1.67-1.41 (m, 6H), 1.33 (s, 6H), 0.89 (s, 18H), 0.68 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 127.2, 99.9, 68.8, 63.8, 44.1, 42.8, 39.3, 26.2, 25.9, 18.3, -3.7, -4.2. FTIR (neat): υ 3078, 2989, 2945, 2929, 2882, 2856, 1641, 1472, 1462, 1434, 1377, 1253, 1223, 1168, 1112, 1061, 1003, 948, 912, 833 cm^{-1}. HRMS (CI) Calcd. for $C_{28}H_{57}O_4Si_2$ $[M+H]^+$: 513.3795, Found: 513.3804.

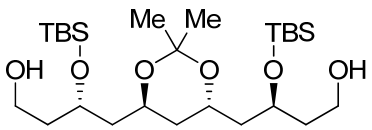
^{1}H NMR



^{13}C NMR



(3*S*,3'*S*)-4,4'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(3-(*tert*-butyldimethylsilyloxy)butan-1-ol)

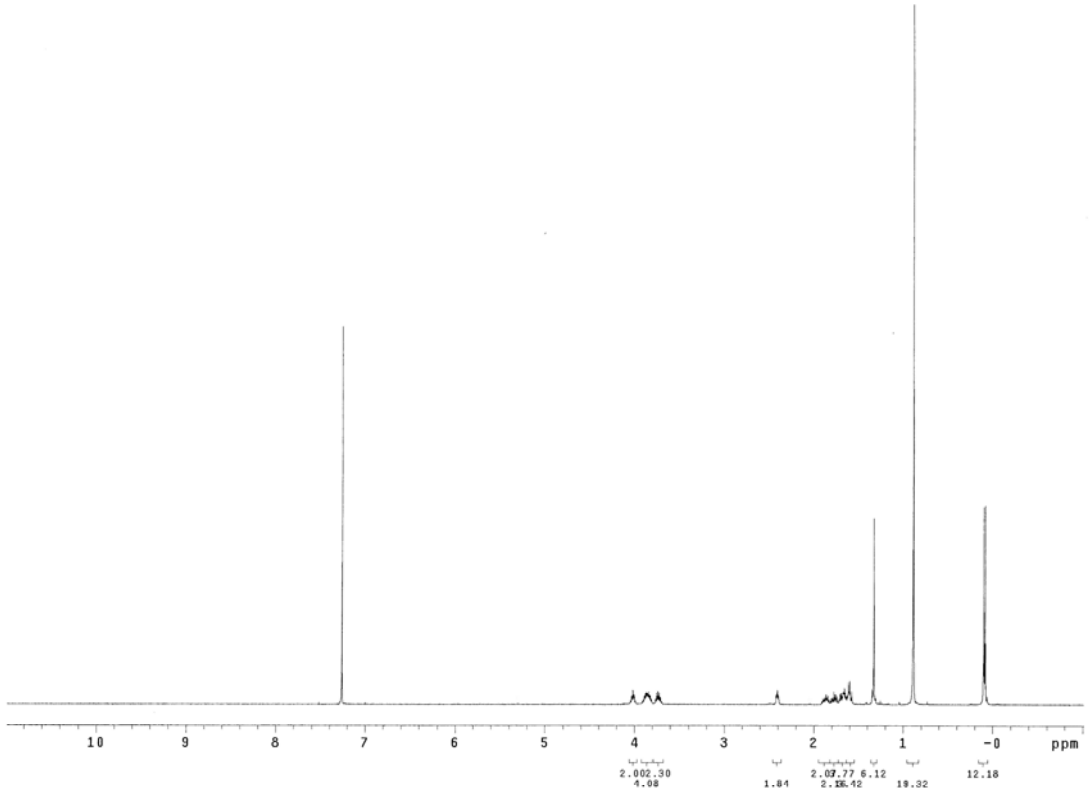


4.7

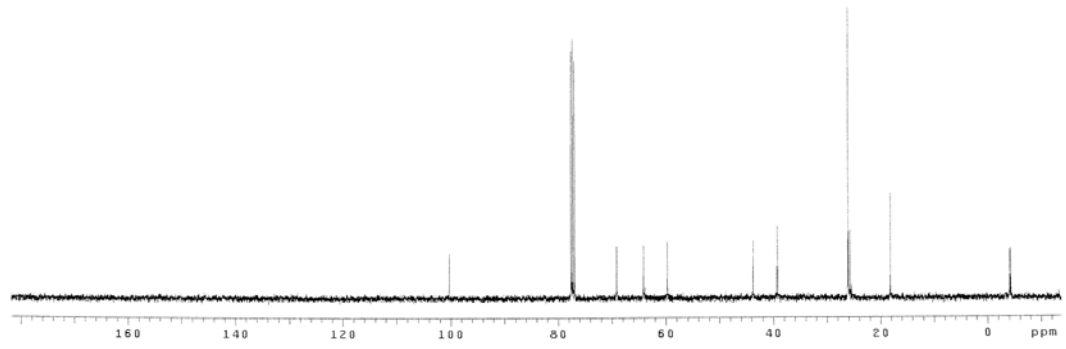
To a stirred solution of **4.6** (0.58 g, 1.132 mmol, 100 mol%) in DCM/MeOH (1:1, 57 mL, 0.02 M) was bubbled ozone at −78 °C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (0.43 g, 11.32 mmol, 1000 mol%) was added in one portion at –78 °C and the resulting solution was slowly warmed to ambient temperature. The mixture was stirred for 12 hr at ambient temperature, and then quenched with H_2O (5 mL). The resulting solution was then concentrated and extracted with DCM (20 mL × 2). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:3 to 1:1 with 0.1% TEA) to give the diol **4.7** (0.50 g, 0.962 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.24 (ethyl acetate:hexanes, 1:2). $[\alpha]_D^{26}$ = +28.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.01-3.93 (m, 2H), 3.90-3.71 (m, 4H), 3.70-3.65 (m, 2H), 2.40 (br s, 2H), 1.86-1.53 (m, 10H), 1.31 (s, 6H), 0.85 (s, 18H), 0.67 (s, 6H), 0.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.3, 69.1, 64.1, 59.7, 43.7, 39.4, 39.2, 26.1, 26.0, 25.7, 18.2, -4.1, -4.3. FTIR (neat): υ 3398, 2986, 2951, 2992, 2882, 2856, 2242, 1472, 1462, 1429, 1379, 1252, 1223, 1165, 1055, 1005, 938, 909 cm^{-1}. HRMS (CI) Calcd. for $C_{26}H_{57}O_6Si_2$ $[M+H]^+$: 521.3694, Found: 521.3691.

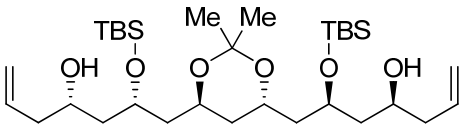
^{1}H NMR



^{13}C NMR



(4*S*,4'*S*,6*S*,6'*S*)-7,7'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(6-(*tert*-butyldimethylsilyloxy)hept-1-en-4-ol)



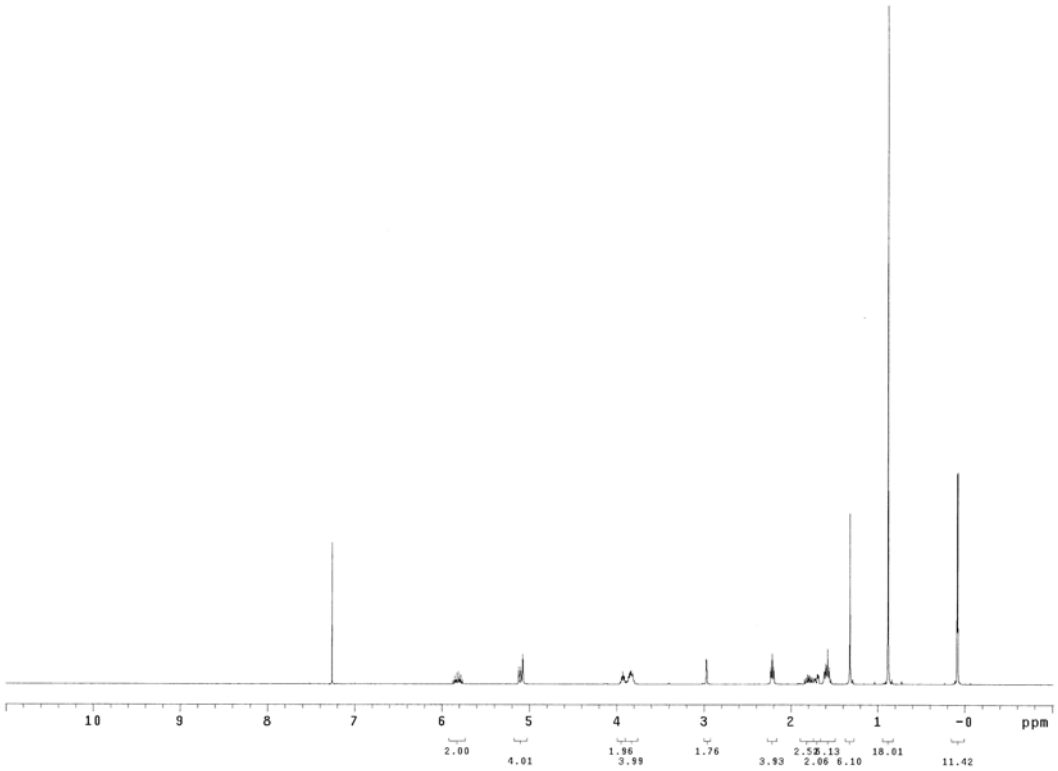
4.8

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (32.2 mg, 0.048 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (62.5 mg, 0.096 mmol, 10 mol%), Cs_2CO_3 (0.125 g, 0.384 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (39 mg, 0.192 mmol, 20 mol%) was added THF (2.4 mL) followed by allyl acetate (1.04 mL, 9.599 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. The diol **4.7** (0.5 g, 0.960 mmol, 100 mol%) in THF (2.4 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 110 ^{o}C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:5 to 1:3 with 0.1% TEA) provided **4.8** (0.45 g, 0.749 mmol, dr > 20:1) as pale yellow oil in 78% yield.

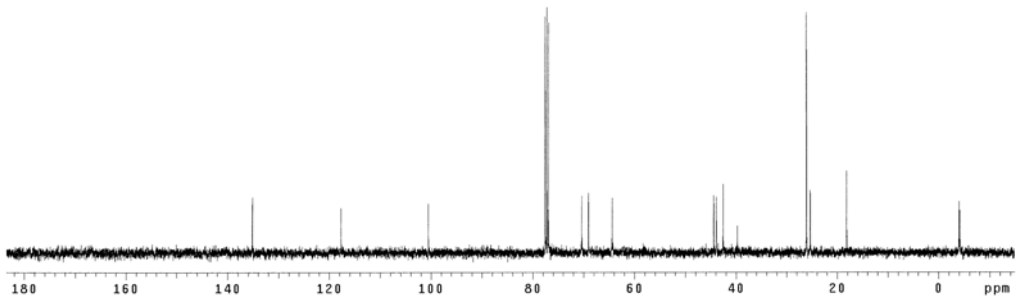
TLC (SiO_2): R_f = 0.28 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +15.0 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87-5.76 (m, 2H), 5.12-5.07 (m, 4H), 3.94-3.81 (m, 6H), 2.99 (s, 2H), 2.21 (t, *J* = 6.4 Hz, 4H), 1.85-1.76 (m, 2H), 1.74-1.68 (m, 2H), 1.62-1.53 (m, 6H), 1.32 (s, 6H), 0.88 (s, 18H), 0.79 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 117.7, 100.5, 70.3, 69.0, 64.4, 44.4, 43.9, 42.6, 39.8, 26.1, 25.3, 18.1, -4.0, -4.1. FTIR (neat): υ 3432, 3075, 2948, 2928, 2856, 2030, 1720, 1641, 1472, 1462, 1429, 1379, 1359,

1251, 1223, 1165, 1115, 1063, 1003, 938, 912 cm^{-1}. HRMS (CI) Calcd. for $C_{32}H_{65}O_6Si_2$ $(M+H)^+$: 601.4320, Found: 601.4318.

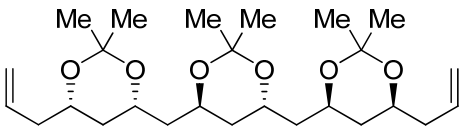
^1H NMR



^{13}C NMR



(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(4-allyl-2,2-dimethyl-1,3-dioxane)



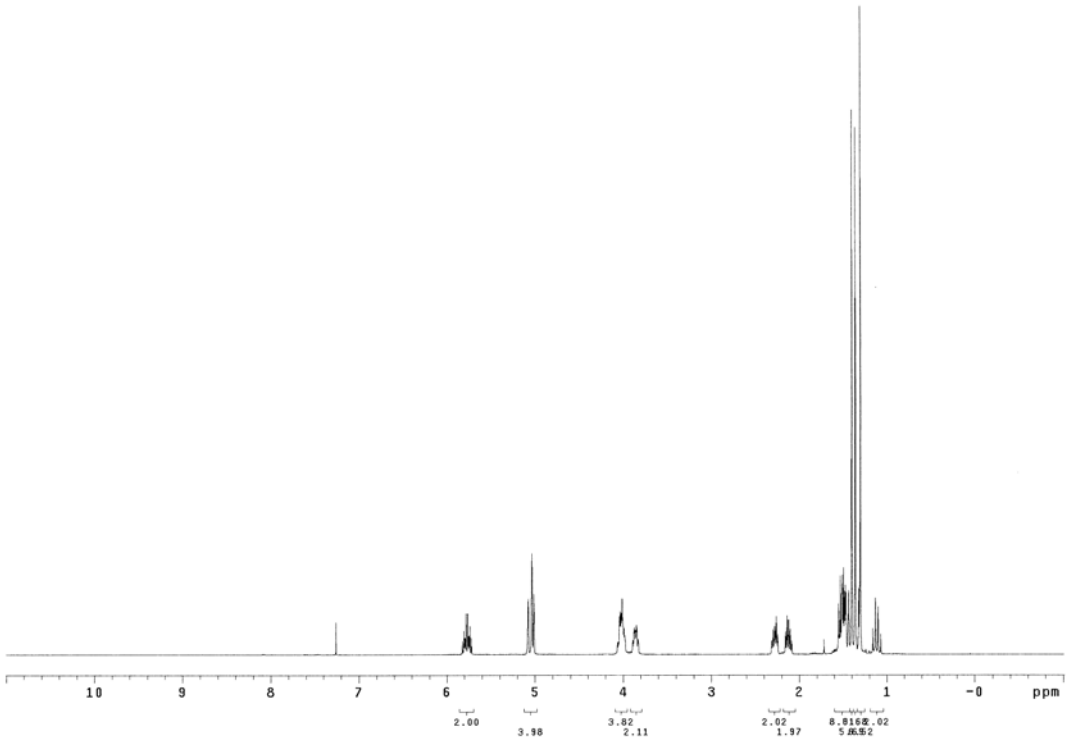
4.9

To a stirred solution of **4.8** (0.4 g, 0.666 mmol, 100 mol%) in methanol (6.7 mL, 0.1 M) was added *p*-toluenesulfonic acid monohydrate (12.7 mg, 0.067 mmol, 10 mol%). The reaction mixture was stirred for 1 hr at ambient temperature. TLC analysis showed complete consumption of the starting material. The reaction mixture was diluted with 2,2-dimethoxypropane (8.2 mL, 66.55 mmol, 10000 mol%) and stirred for 1 hr at ambient temperature. After concentrated in vacuo, the residue was diluted with 2,2-dimethoxypropane (4.1 mL, 33.28 mmol, 5000 mol%) and stirred for 1 hr at ambient temperature. The reaction mixture was again concentrated in vacuo. 2,2-Dimethoxypropane (4.1 mL, 33.28 mmol, 5000 mol%) was added and the reaction mixture was stirred for 1 hr at ambient temperature. The reaction mixture was diluted with EtOAc (30 mL) and washed with saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:15 with 0.1% TEA) to give **4.9** (0.28 g, 0.619 mmol) as a colorless oil in 93% yield.

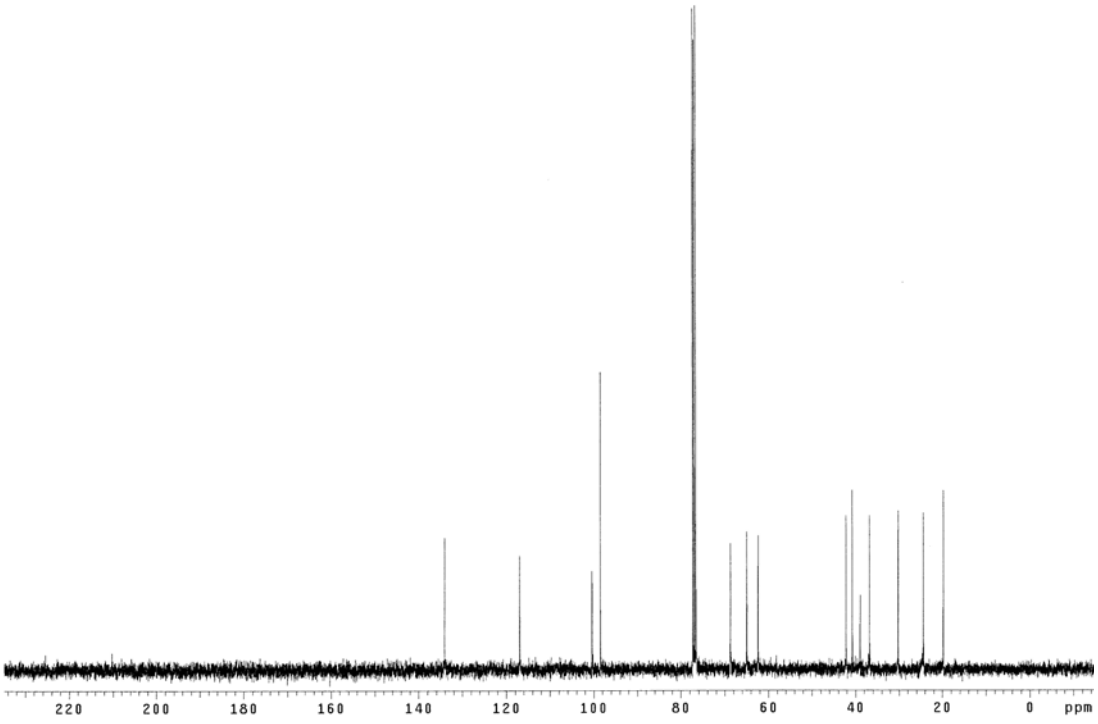
TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexanes, 1:10). $[\alpha]_D^{26}$ = +18.5 (*c* = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.82-5.72 (m, 2H), 5.08-5.01 (m, 4H), 4.06-3.98 (m, 4H), 3.89-3.83 (m, 2H), 2.31-2.25 (m, 2H), 2.16-2.09 (m, 2H), 1.55-1.46 (m, 8H), 1.40 (s,

6H), 1.36 (s, 6H), 1.30 (s, 6H), 1.16-1.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 117.0, 100.4, 98.5, 68.7, 64.9, 62.4, 42.2, 40.8, 39.0, 36.8, 30.2, 24.4, 19.8. FTIR (neat): υ 2989, 2941, 2907, 2860, 2239, 2106, 1736, 1642, 1460, 1431, 1373, 1350, 1223, 1199, 1143, 1111, 1024, 981, 939, 911, 881, 812 cm^{-1}. HRMS (CI) Calcd. for $C_{26}H_{45}O_6$ $[M+H]^+$: 453.3216, Found: 453.3216.

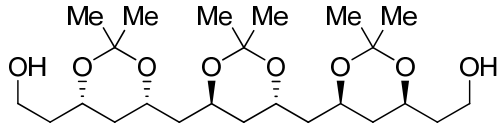
^{1}H NMR



^{13}C NMR



2,2'-(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(2,2-dimethyl-1,3-dioxane-6,4-diyl)diethanol



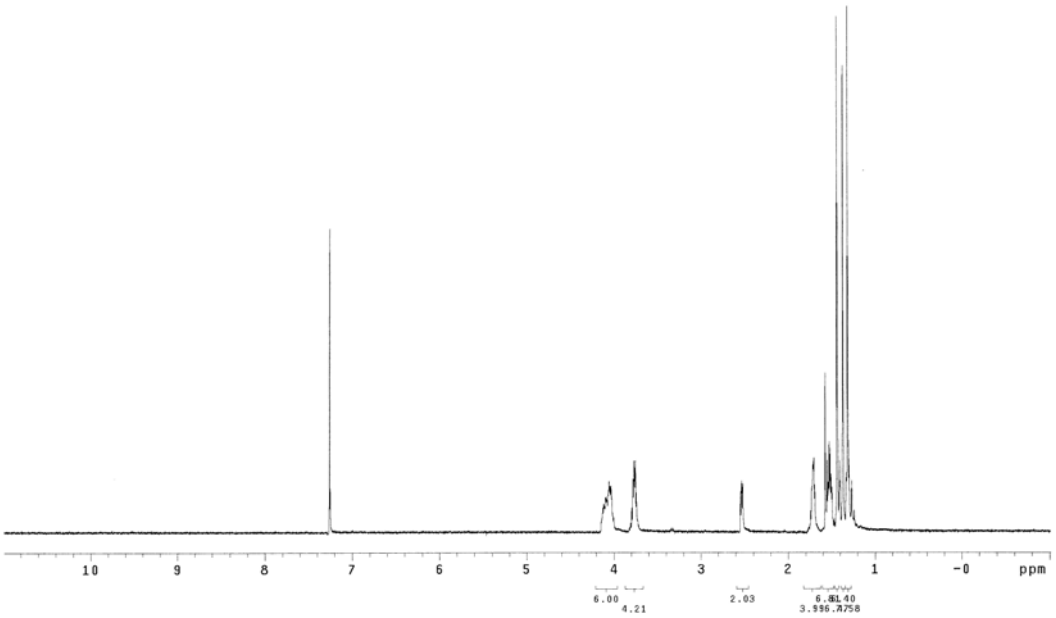
4.10

To a stirred solution of **4.9** (0.15 g, 0.331 mmol, 100 mol%) in in DCM/MeOH (1:1, 17 mL, 0.02 M) was bubbled ozone at −78 ^{o}C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (0.0.125 g, 3.31 mmol, 1000 mol%) was added in one portion at –78 ^{o}C and the resulting solution was

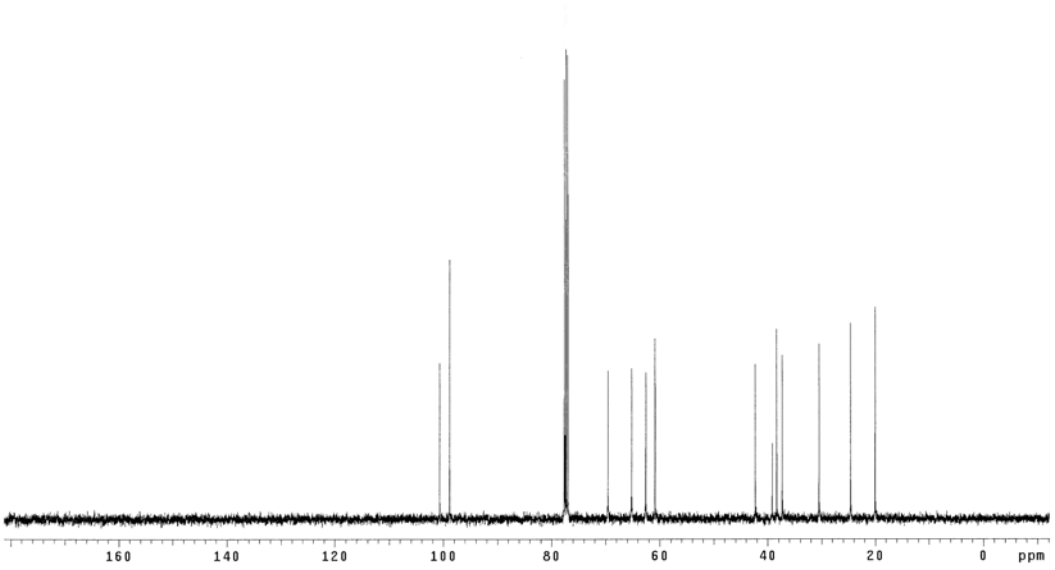
warmed to ambient temperature slowly. The mixture was stirred for 12 hr at ambient temperature, and then quenched with H_2O (5 mL). The resulting mixture was concentrated and extracted with DCM (20 mL × 2). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 to ethyl acetate:methanol 1:20 with 0.1% TEA) to give the diol **4.10** (0.119 g, 0.258 mmol) as a colorless syrup in 78% yield.

TLC (SiO_2): R_f = 0.20 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +72.5 (*c* = 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.13-4.02 (m, 6H), 3.81-3.74 (m, 4H), 2.55-2.52 (m, 2H), 1.74-1.70 (m, 4H), 1.58-1.50 (m, 6H), 1.44 (s, 6H), 1.43-1.38 (m, 2H), 1.37 (s, 6H), 1.30 (s, 6H), 1.32-1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.7, 98.9, 77.5, 69.6, 65.2, 62.6, 60.9, 42.3, 39.1, 38.3, 37.3, 30.5, 24.6, 20.1. FTIR (neat): υ 3400, 2990, 2942, 2917, 2882, 1467, 1422, 1380, 1346, 1242, 1222, 1198, 1167, 1137, 1095, 1049, 1010, 936, 910, 875, 824 cm^{-1}. HRMS (CI) Calcd. for $C_{24}H_{45}O_8$ $[M+H]^+$: 461.3114, Found: 461.3111.

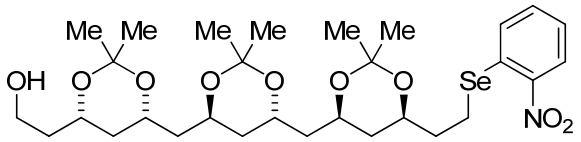
^{1}H NMR



^{13}C NMR



2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-(2-(2-nitrophenylselanyl)ethyl)-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol



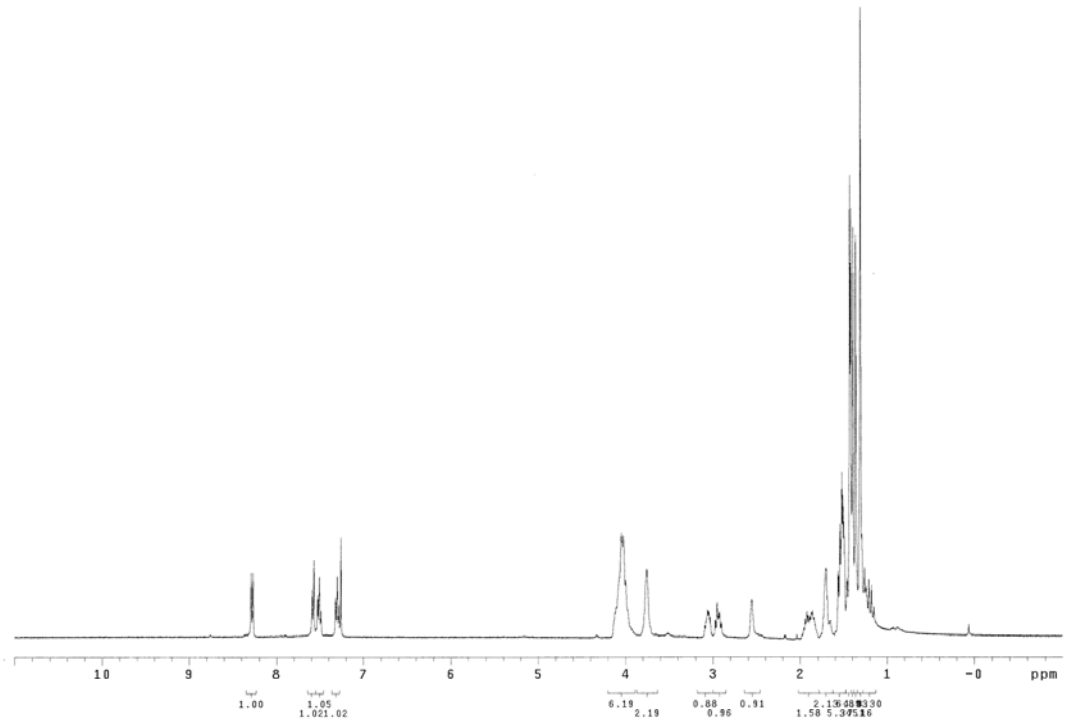
4.11

To a stirred solution of the alcohol **4.10** (288 mg, 0.626 mmol, 100 mol%) in THF (3.1 mL, 0.2 M) were added 2-nitrophenyl selenocyanate (156 mg, 0.689 mmol, 110 mol%) and freshly distilled *n*-tributylphosphine (0.17 mL, 0.689 mmol, 110 mol%). The reaction mixture was stirred for 4 hr at ambient temperature and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:15 to 1:10 with 0.1% TEA) to give the selenide **4.11** (202 mg, 0.313 mmol) as a brownish oil in 50% yield and the starting diol **4.10** (61 mg, 0.131 mmol, 21% recovered yield). The recovered diol **4.10** was subjected to second round of mono-selenylation to **4.11** (29 mg, 0.066 mmol, 10% yield).

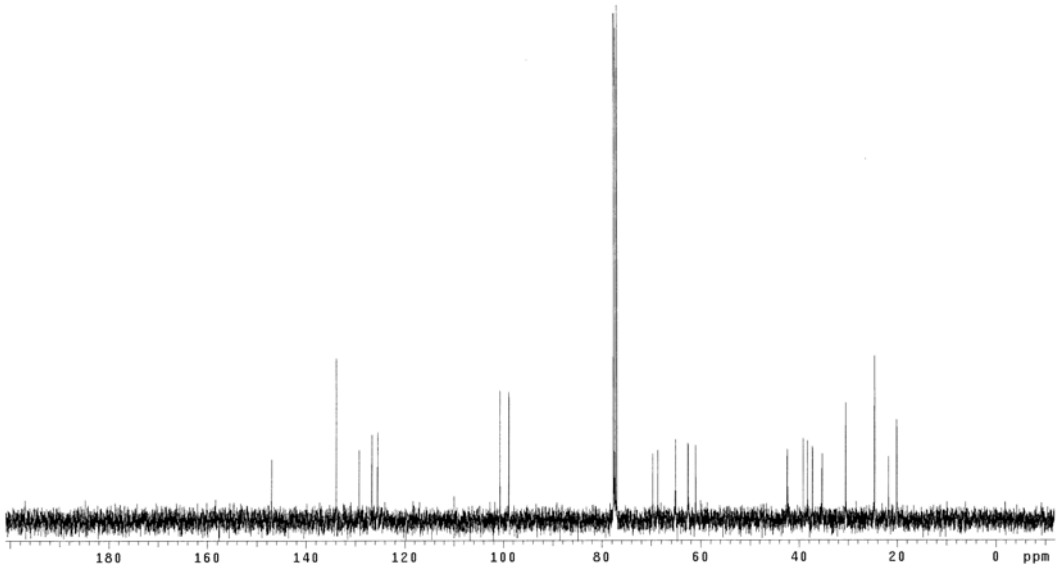
TLC (SiO_2): R_f = 0.20 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +2.47 (*c* = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.16-3.88 (m, 6H), 3.82-3.68 (m, 2H), 3.10-3.03 (m, 1H), 2.97-2.90 (m, 1H), 2.56 (br s, 1H), 1.95-1.84 (m, 2H), 1.74-1.69 (m, 2H), 1.56-1.46 (m, 6H), 1.43 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 6H), 1.29-1.15 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 133.6, 133.5, 129.0, 126.5, 125.3, 100.5,

98.7, 98.6, 77.2, 69.7, 68.4, 64.9, 62.4, 62.3, 61.0, 42.2, 42.1, 38.9, 38.0, 37.0, 35.1, 30.3, 30.2, 24.4, 21.5, 19.9, 19.8. FTIR (neat): υ 2945, 1591, 1514, 1381, 1333, 1304, 1248, 1224, 1201, 1166, 1038 cm^{-1}. HRMS (CI) Calcd. for $C_{30}H_{48}NO_9Se$ $[M+H]^+$: 646.2494, Found: 646.2497.

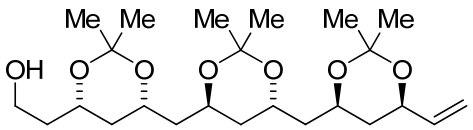
^1H NMR



^{13}C NMR



2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-vinyl-1,3-dioxan-4-yl)methyl)-2,2 dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol

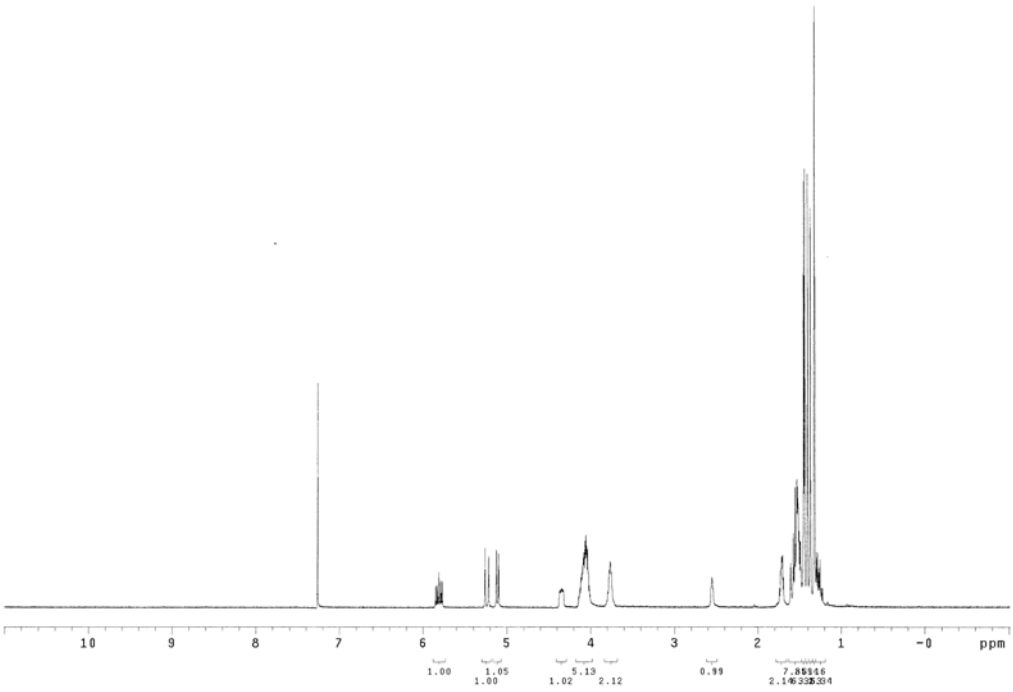


4.IV

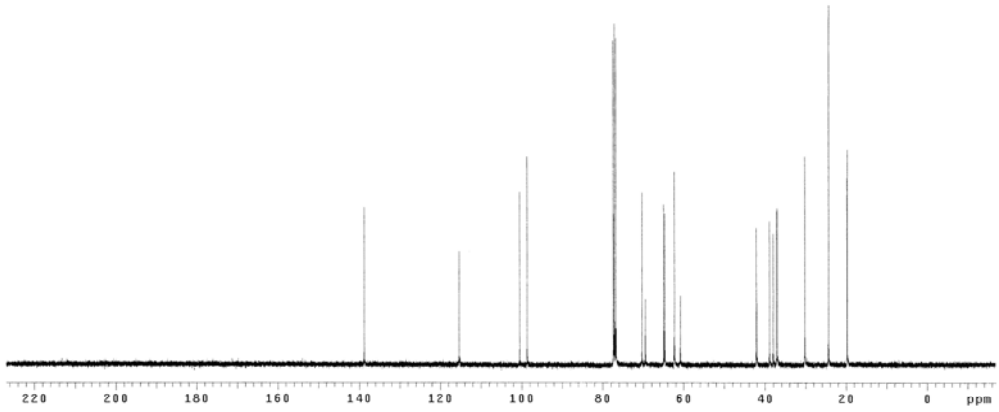
To a stirred solution of the selenide **4.11** (420 mg, 0.651 mmol, 100 mol%) in THF (13 mL, 0.05 M) were added $NaHCO_3$ (164 mg, 1.953 mmol, 300 mol%) and H_2O_2 (0.71 mL, 500 mol%, 30% w/w in H_2O). The reaction mixture was stirred for 24 hr at ambient temperature and extracted with EtOAc. The combined organic extracts was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue

was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:3 with 0.1% TEA) to give the allylic ether **4.IV** (251 mg, 0.566 mmol) as a colorless oil in 87% yield. TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +11.3 (*c* = 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.37-4.33 (m, 1H), 4.14-4.01 (m, 5H), 3.78-3.75 (m, 2H), 2.55 (br s, 1H), 1.74-1.70 (m, 2H), 1.61-1.46 (m, 8H), 1.45 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 1.30-1.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 115.3, 100.4, 98.6, 70.3, 69.5, 64.9, 64.7, 62.3, 60.8, 42.1, 42.1, 38.9, 38.0, 37.1, 37.0, 30.3, 30.2, 24.4, 19.8, 19.7. FTIR (neat): υ 3491, 2989, 2942, 2915, 1380, 1250, 1224, 1200, 1169, 1142, 1040, 1013, 992, 938, 916, 874, 827, 792 cm^{-1}. HRMS (CI) Calcd. for $C_{24}H_{43}O_7$ $[M+H]^+$: 443.3009, Found: 443.3011.

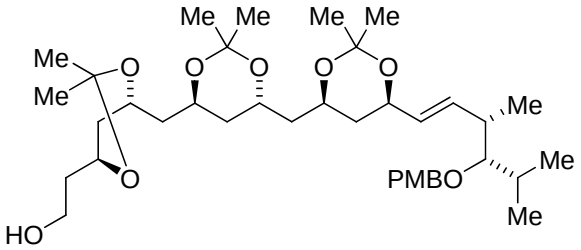
^1H NMR



^{13}C NMR



2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol



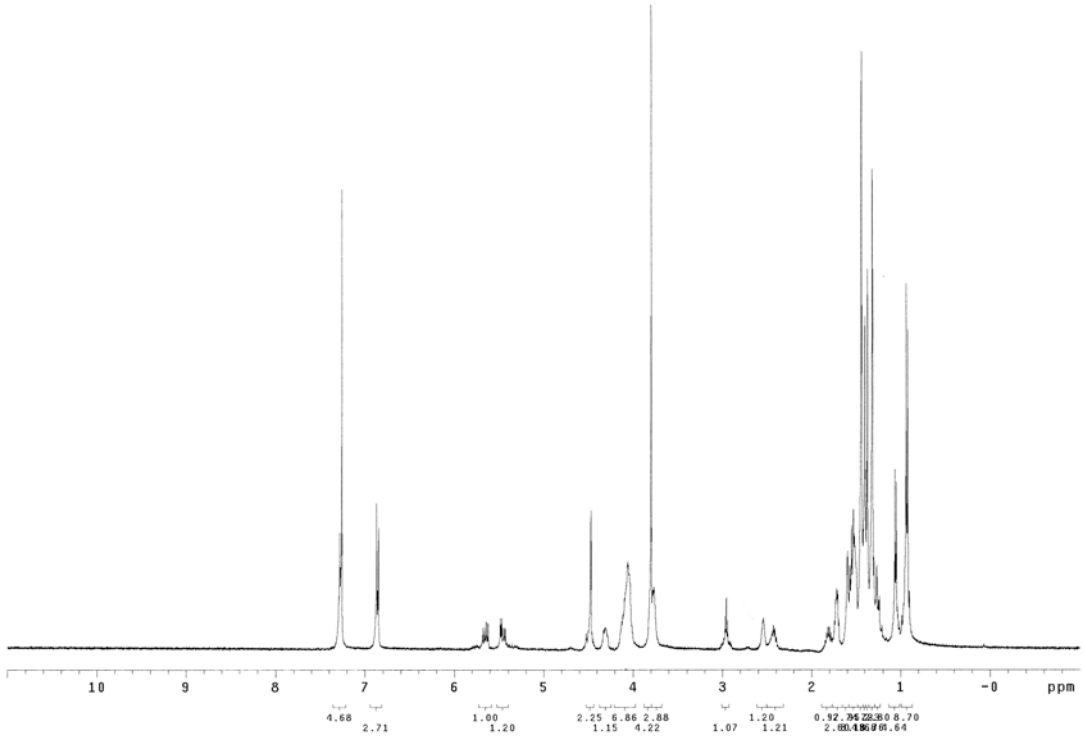
4.13

To a stirred solution of **4.IV** (245 mg, 0.554 mmol, 100 mol%) and **4.12**(413 mg, 1.662 mmol, 300 mol%) in DCM (5.5 mL, 0.1 M) was added Hoveyda-Grubbs catalyst 2nd generation (35 mg, 0.055 mmol, 10 mol%). The reaction mixture was stirred for 24 hr at 40 ^{o}C and concentrated in vacuo. Purification of the product by column

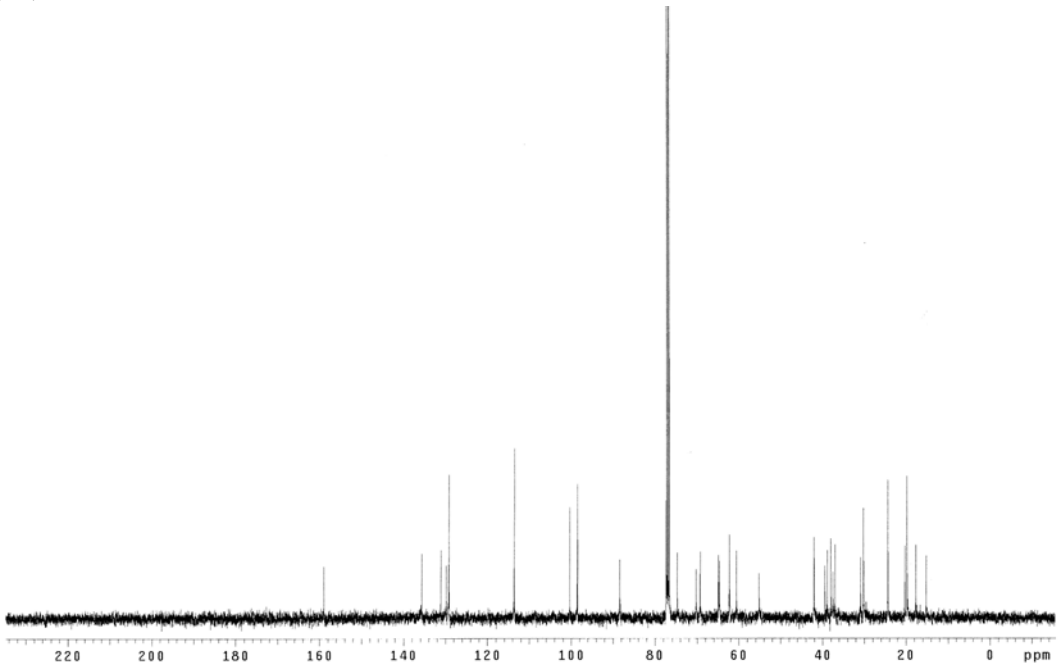
chromatography (SiO_2: ethyl acetate:hexanes 1:3 with 0.1% TEA) provided **4.13** (195 mg, 0.29 mmol) as pale yellow oil in 53% yield.

TLC (SiO_2): R_f = 0.50 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +11.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.86 (dd, *J* = 6.8, 2.0 Hz, 2H), 5.65 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.46 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.47 (s, 2H), 4.36-4.27 (m, 1H), 4.14-4.02 (m, 5H), 3.80 (s, 3H), 3.80-3.74 (m, 2H), 2.96 (m, 1H), 2.54 (br s, 1H), 2.48-2.38 (m, 1H), 1.83-1.78 (m, 1H), 1.74-1.70 (m, 2H), 1.60-1.52 (m, 6H), 1.44 (s, 6H), 1.40 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 1.30-1.21 (m, 4H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 135.7, 131.1, 129.8, 129.2, 113.6, 100.4, 98.5, 98.4, 88.4, 74.7, 70.3, 69.3, 64.9, 64.7, 62.3, 60.6, 55.1, 42.1, 39.4, 38.9, 38.2, 38.0, 37.5, 37.0, 30.9, 30.2, 24.3, 20.2, 19.7, 17.7, 15.2. FTIR (neat): υ 2997, 1979, 1674, 1514, 1382, 1215, 1037, 935, 746, 696, 667 cm^{-1}. HRMS (CI) Calcd. for $C_{38}H_{61}O_9$ $[M-H]^+$: 661.4316, Found: 661.4323

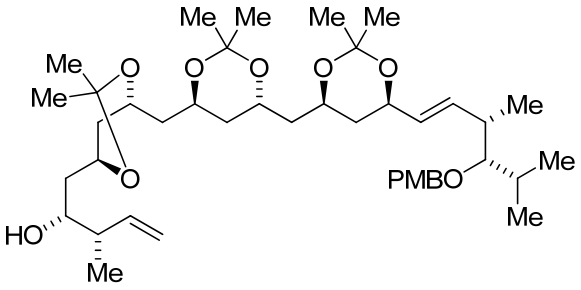
^{1}H NMR



^{13}C NMR



(2*R*,3*S*)-1-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-ol



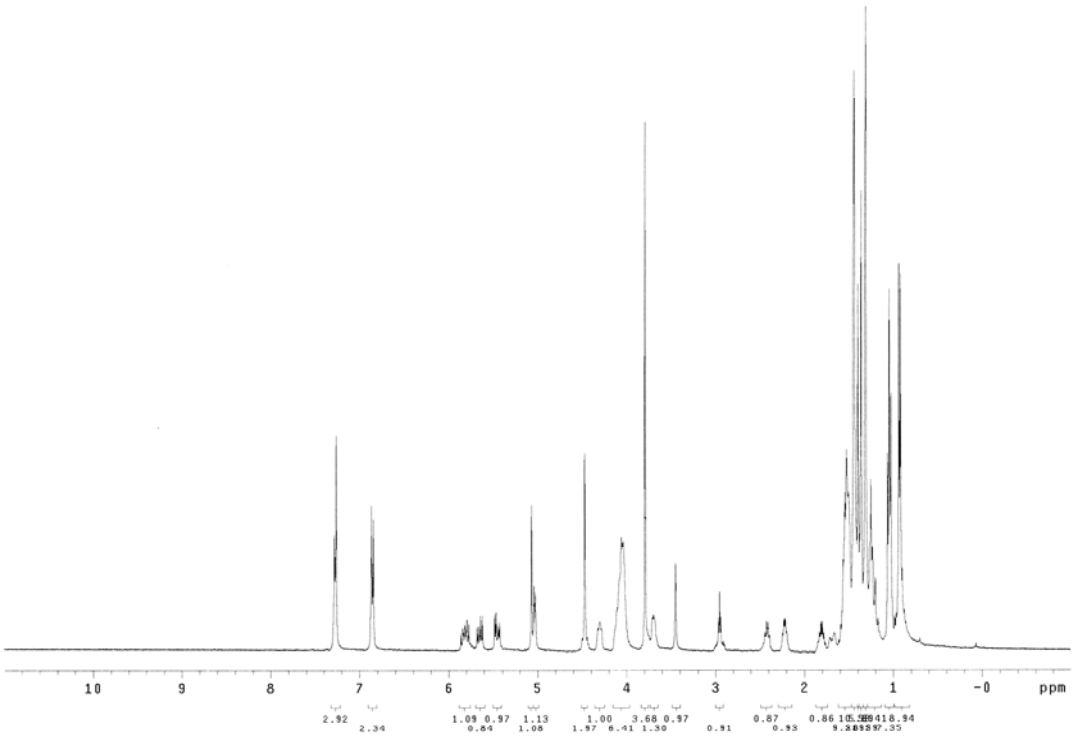
4.II

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with alcohol **4.13** (133 mg, 0.2 mmol, 100 mol%), *(S)*-**II**[11k] (20.7 mg, 0.02 mmol, 10 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and crotyl acetate (68 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:7 with 0.1% TEA) provided **4.II** (121.9 mg, 0.17 mmol) as a yellow oil in 85% yield (14:1 dr).

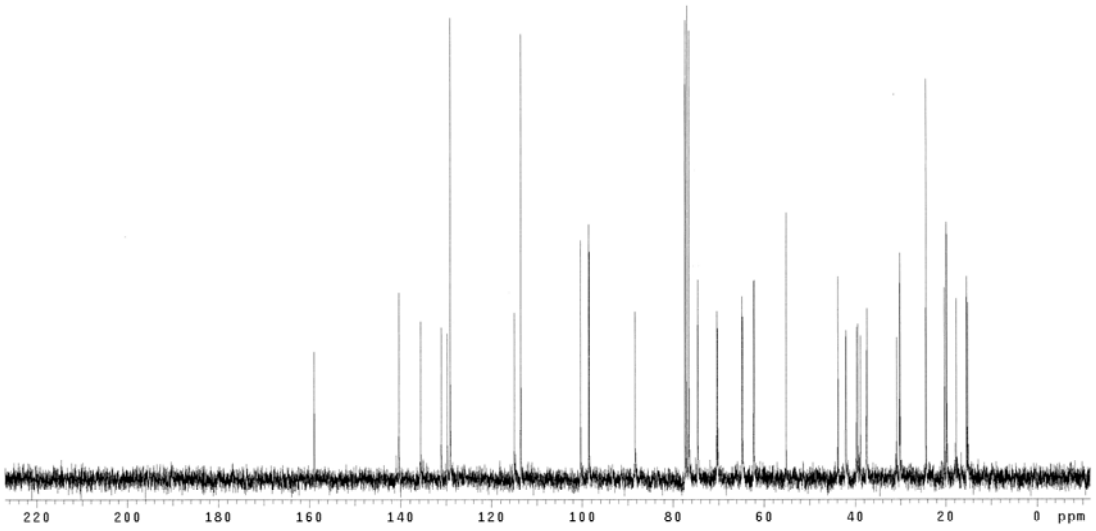
TLC (SiO_2): R_f = 0.65 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +98.0 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.86-5.77 (m, 1H), 5.65 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.46 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.07 (s, 1H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.47 (s, 2H), 4.34-4.26 (m, 1H), 4.14-3.98 (m, 5H), 3.79 (s, 3H),

3.72-3.66 (m, 1H), 3.45 (s, 1H), 2.97-2.94 (m, 1H), 2.44-2.39 (m, 1H), 2.24-2.20 (m, 1H), 1.83-1.78 (m, 1H), 1.56-1.46 (m, 8H), 1.45 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.32 (s, 6H), 1.30-1.20 (m, 4H), 1.05 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 140.4, 135.7, 131.1, 129.8, 129.2, 115.0, 113.6, 100.3, 98.6, 98.5, 88.4, 74.7, 74.6, 70.4, 70.2, 64.9, 64.7, 62.3, 62.2, 55.1, 43.8, 42.1, 42.0, 39.7, 39.4, 38.9, 37.5, 37.4, 30.9, 30.2, 30.1, 24.3, 20.2, 19.8, 19.8, 17.7, 15.4, 15.2. FTIR (neat): υ 3502, 2987, 2943, 1940, 1737, 1613, 1514, 1461, 1431, 1380, 1301, 1247, 1224, 1200, 1168, 1127, 1087, 1037, 980, 936, 913, 874, 823, 702 cm^{-1}. HRMS (CI) Calcd. for $C_{42}H_{67}O_9$ $[M-H]^+$: 715.4786, Found: 715.4786

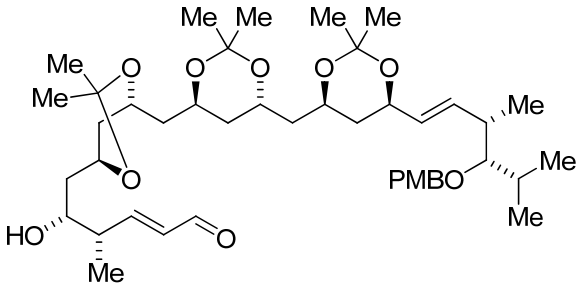
^{1}H NMR



^{13}C NMR



(4*S*,5*R*,*E*)-5-hydroxy-6-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylhex-2-enal



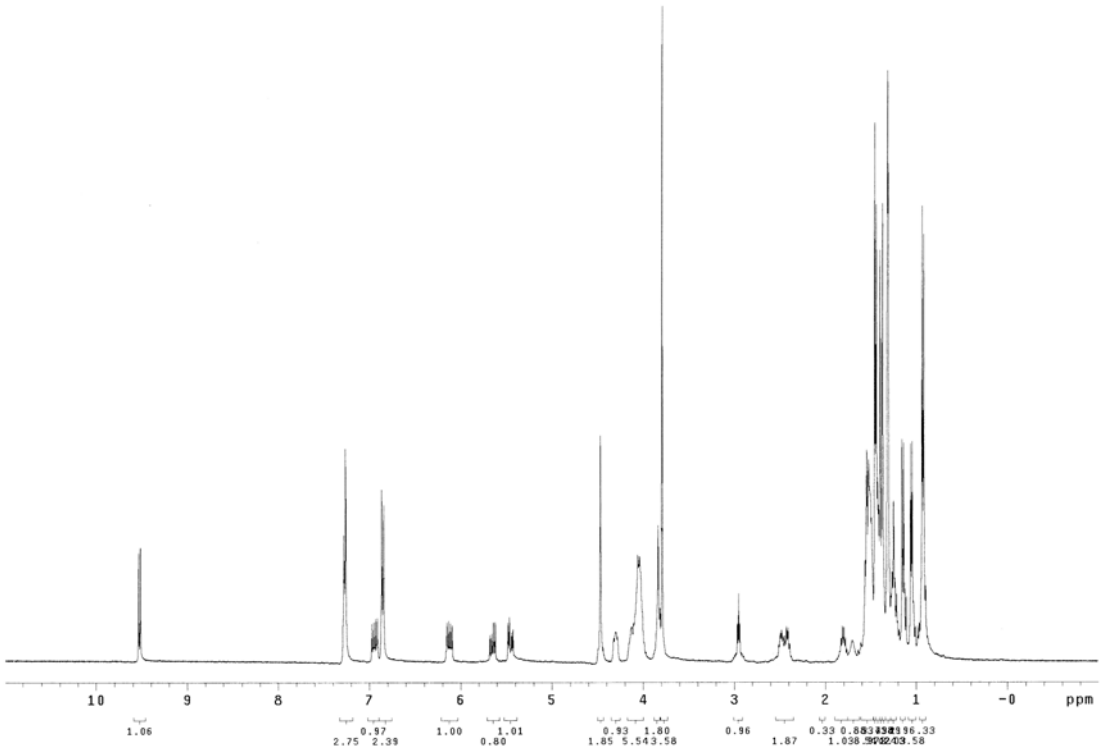
4.14

To a stirred solution of **4.II** (122 mg, 0.170 mmol, 100 mol%) and acrolein (48 mg, 0.85 mmol, 500 mol%) in DCE (1.7 mL, 0.1 M) was added Hoveyda-Grubbs catalyst 2nd generation (8.0 mg, 0.013 mmol, 7.5 mol%). The reaction mixture was stirred for 24

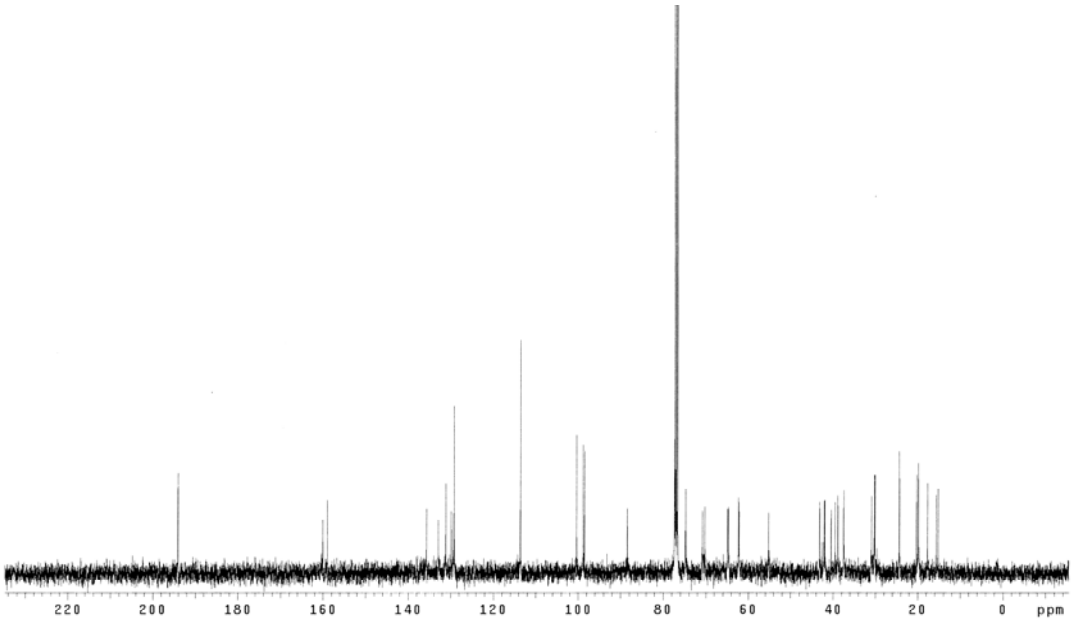
hr at 60 ^{o}C. Acrolein (48 mg, 0.85 mmol, 500 mol%) and Hoveyda-Grubbs catalyst 2nd generation (8.0 mg, 0.013 mmol, 7.5 mol%) were added and the reaction mixture was stirred for 24 hr at 60 ^{o}C. The reaction mixture was concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 with 0.1% TEA) provided the starting material **4.II** (37 mg, 0.051mmol, 30% recovered yield) and the product **4.14** (66 mg, 0.09 mmol, 52% yield, 74% BRSM) as a pale yellow oil.

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +70.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.12 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.65 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.45 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.47 (s, 2H), 4.32-4.27 (m, 1H), 4.12-3.98 (m, 5H), 3.86-3.80 (m, 2H), 3.79 (s, 3H), 2.97-2.93 (m, 1H), 2.49-2.40 (m, 2H), 1.83-1.77 (m, 1H), 1.56-1.46 (m, 8H), 1.46 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28-1.19 (m, 4H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 160.0, 158.9, 135.7, 132.9, 131.1, 129.8, 129.2, 113.6, 100.4, 98.8, 98.5, 88.4, 74.8, 74.7, 70.8, 70.3, 64.8, 64.7, 62.3, 62.2, 55.2, 43.2, 42.1, 41.9, 40.4, 39.4, 38.8, 37.5, 37.4, 30.9, 30.2, 30.1, 24.3, 20.2, 19.8, 19.7, 17.7, 15.6, 15.2. FTIR (neat): υ 3508, 2987, 2940, 1690,1613, 1514, 1459, 1380, 1301, 1247, 1224, 1200, 1168, 1127, 1085, 1036, 977, 936, 874, 821, 732 cm^{-1}. HRMS (CI) Calcd. for $C_{43}H_{67}O_{10}$ $[M-H]^+$: 743.4734, Found: 743.4738.

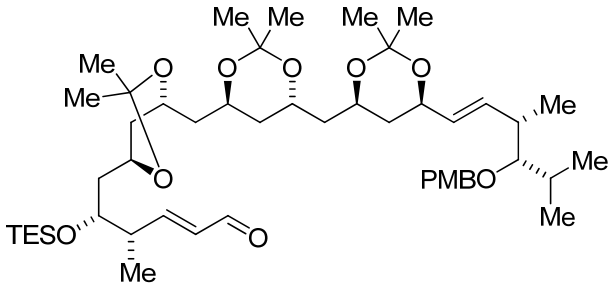
^{1}H NMR



^{13}C NMR



3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal



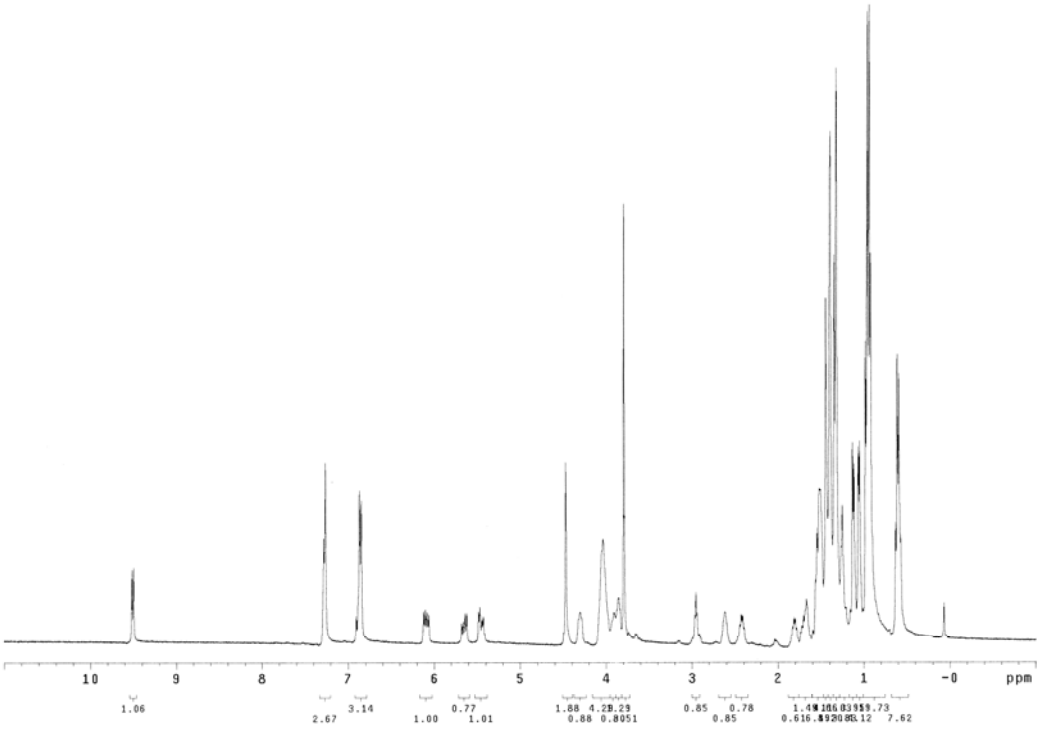
4.15

To a stirred solution of **4.14** (37 mg, 0.05 mmol, 100 mol%) in DCM (0.5 mL, 0.1 M) were added 2,6-lutidine (23 μL, 0.2 mmol, 400 mol%) and TESOTf (23 μL, 0.1 mmol, 200 mol%) at -78 ^{o}C. The reaction mixture was stirred for 2 hr at -78 ^{o}C, and then quenched with saturated aq. $NaHCO_3$ (2 mL). The reaction mixture was extracted with DCM. The combined organic extracts wase washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:10 with 0.1% TEA) to give **4.15** (38 mg, 0.044 mmol) as a yellow oil in 87% yield.

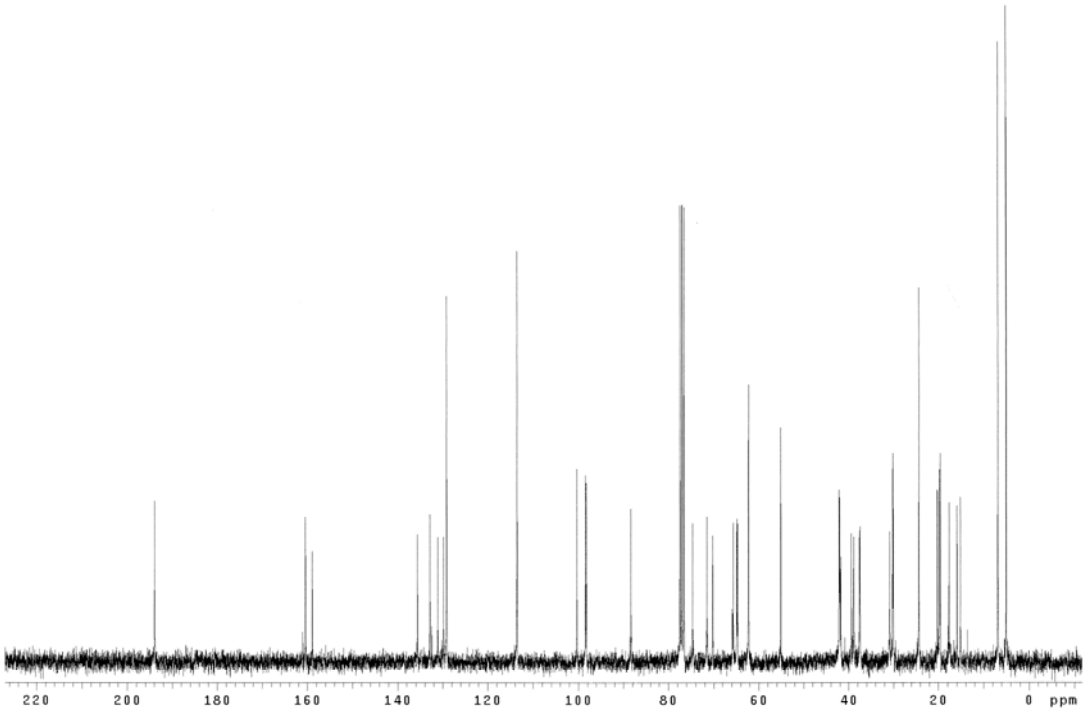
TLC (SiO_2): R_f = 0.60 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +29.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.90-6.85 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.09 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.65 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.45 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.47 (s, 2H), 4.34-4.26 (m, 1H), 4.10-3.96 (m, 4H), 3.95-3.88 (m, 1H), 3.88-3.82 (m, 1H), 3.79 (s, 3H), 2.97-2.94 (m, 1H), 2.66-2.58 (m, 1H), 2.46-2.38 (m, 1H), 1.84-1.76 (m, 1H), 1.56-1.46 (m, 8H), 1.44 (s, 3H), 1.39 (s,

6H), 1.34 (s, 3H), 1.32 (s, 6H), 1.28-1.21 (m, 4H), 1.12 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 0.98-0.92 (m, 15H), 0.63 (q, J = 7.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 160.4, 158.9, 135.6, 132.9, 131.1, 129.8, 129.1, 113.5, 100.3, 98.4, 98.2, 88.4, 74.7, 71.5, 70.2, 65.6, 64.9, 64.7, 62.3, 55.1, 42.1, 42.0, 41.9, 41.8, 39.4, 38.9, 37.6, 37.5,30.8, 30.2, 30.1, 24.3, 20.2, 19.7, 19.6, 17.7, 15.9, 15.1, 6.8, 5.0. FTIR (neat): υ 2987, 2950, 2912, 2876, 1693, 1613, 1514, 1460, 1379, 1301, 1246, 1224, 1199, 1169, 1128, 1083, 1034, 981, 938, 873, 854, 821, 781, 740, 726 cm^{-1}. HRMS (CI) Calcd. for $C_{49}H_{81}O_{10}Si_1$ $[M-H]^+$: 857.5599, Found: 857.5602.

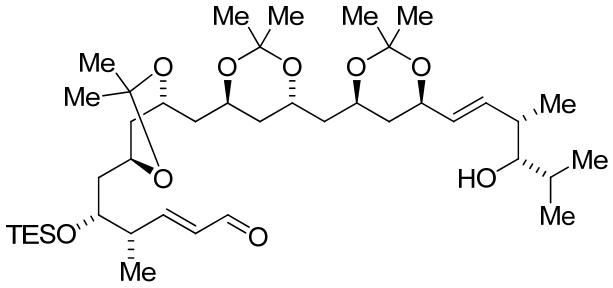
^{1}H NMR



^{13}C NMR



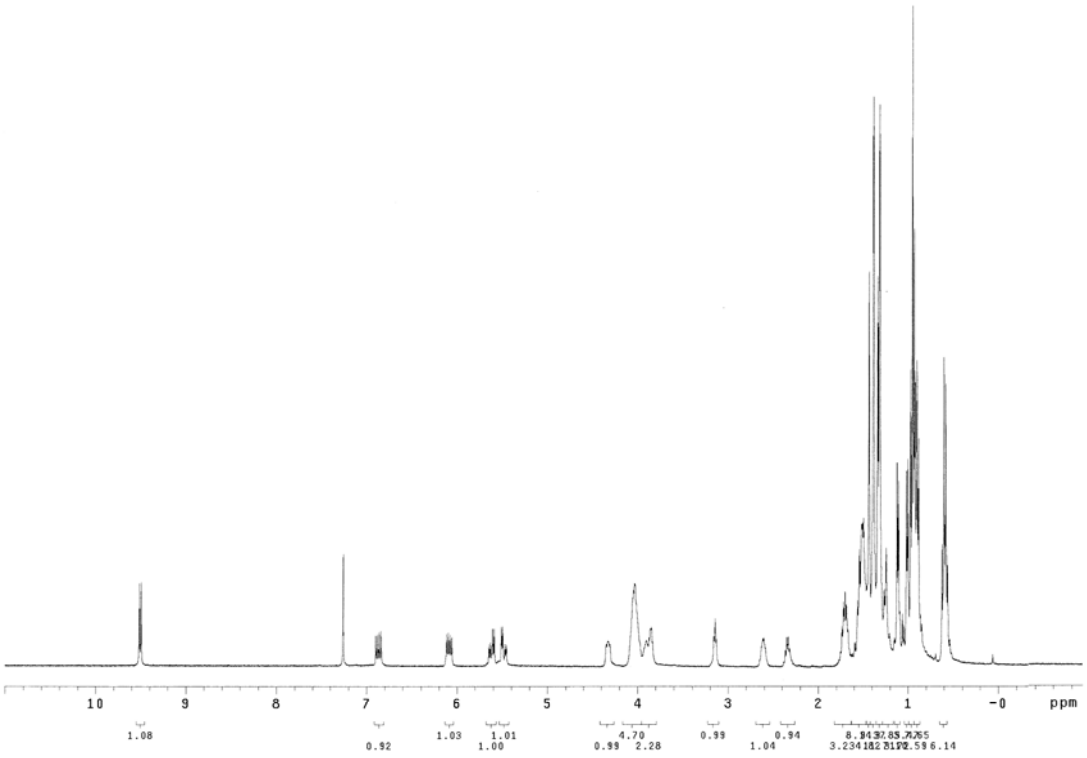
(4*S*,5*R*,*E*)-6-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal



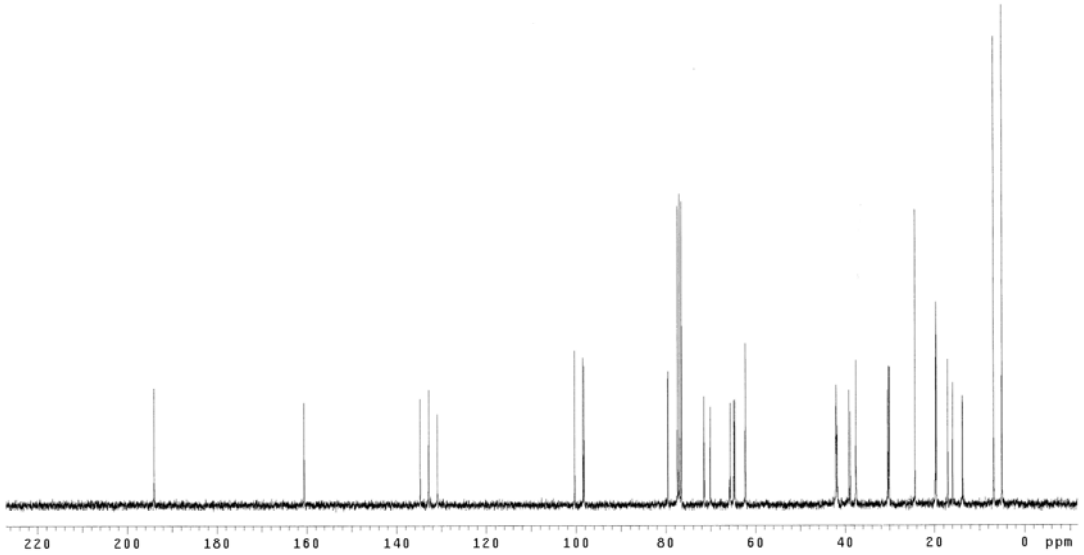
4.16

To a stirred solution of **4.15** (38 mg, 0.044 mmol, 100 mol%) in DCM/H_2O (1.4 mL/0.07 mL, 0.03M) was added DDQ (13 mg, 0.057 mmol, 130 mol%) at 0 ^oC. The reaction mixture was stirred for 2 hr at 0 ^oC, and then quenched with saturated aq. $NaHCO_3$ (0.5 mL). The reaction mixture was extracted with DCM. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:7 to 1:5 with 0.1% TEA) to give **4.16** (28 mg, 0.037 mmol) as a colorless oil in 85% yield. TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +78.0 (*c* = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.09 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.62 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.48 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.34-4.31 (m, 1H), 4.10-3.96 (m, 4H), 3.95-3.87 (m, 1H), 3.87-3.81 (m, 1H), 3.16-3.13 (m, 1H), 2.66-2.57 (m, 1H), 2.36-2.31 (m, 1H), 1.74-1.67 (m, 1H), 1.59-1.45 (m, 8H), 1.44 (s, 3H), 1.39 (s, 6H), 1.34 (s, 3H), 1.32 (s, 6H), 1.28-1.21 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98-0.89 (m, 15H), 0.60 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 160.6, 134.8, 132.9, 130.9, 100.4, 98.5, 98.3, 79.5, 71.6, 70.2, 65.7, 64.9, 64.7, 62.3, 42.2, 42.1, 41.8, 39.2, 38.9, 37.6, 30.4, 30.2, 30.1, 24.3, 19.7, 19.6, 17.0, 15.9, 13.8, 6.8, 5.0. FTIR (neat): υ 3515, 2987, 2950, 2876, 1692, 1634, 1459, 1379, 1224, 1199, 1168, 1142, 1084, 1021, 1006, 981, 938, 913, 874, 855, 816, 781, 731 cm^{-1}. HRMS (CI) Calcd. for $C_{41}H_{73}O_9Si_1$ $[M-H]^+$: 737.5024, Found: 737.5012.

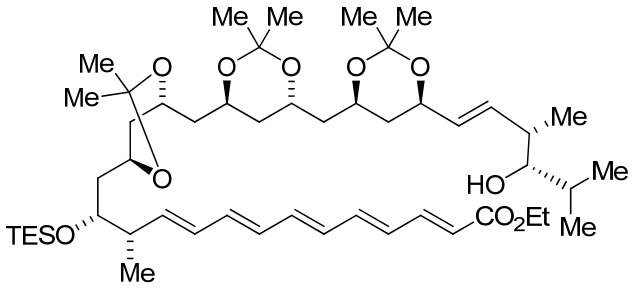
^{1}H NMR



^{13}C NMR



(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*)-ethyl 14-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-12-methyl-13-(triethylsilyloxy)tetradeca-2,4,6,8,10-pentaenoate

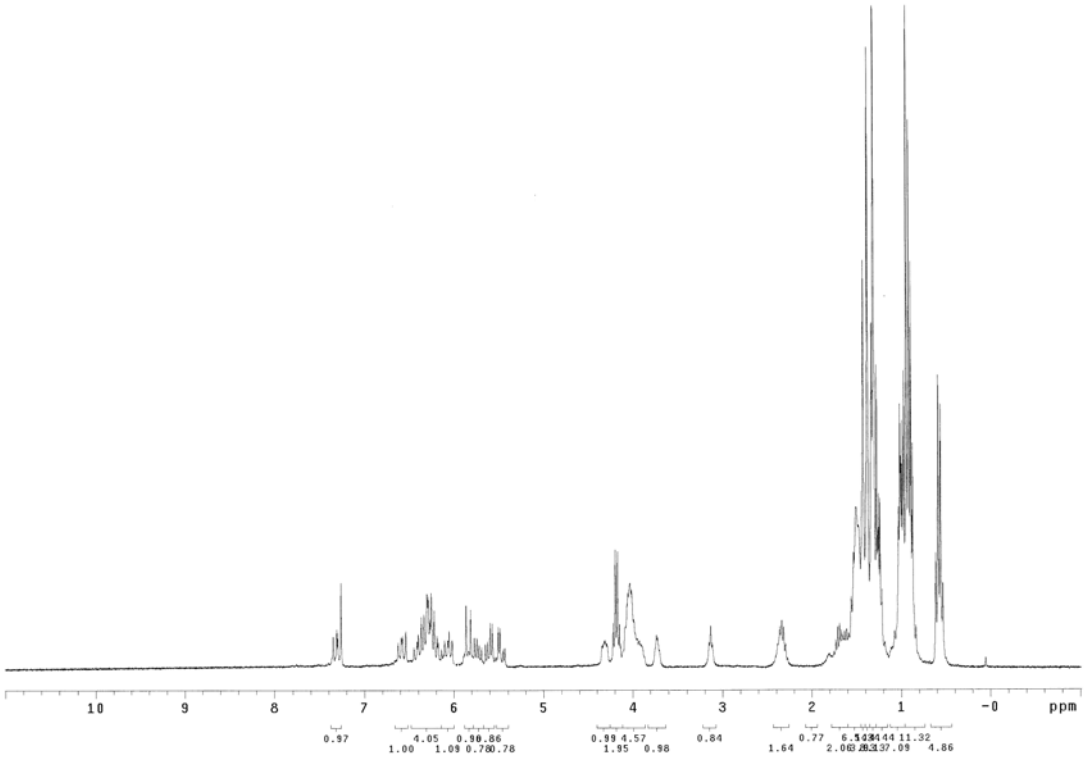


4.17

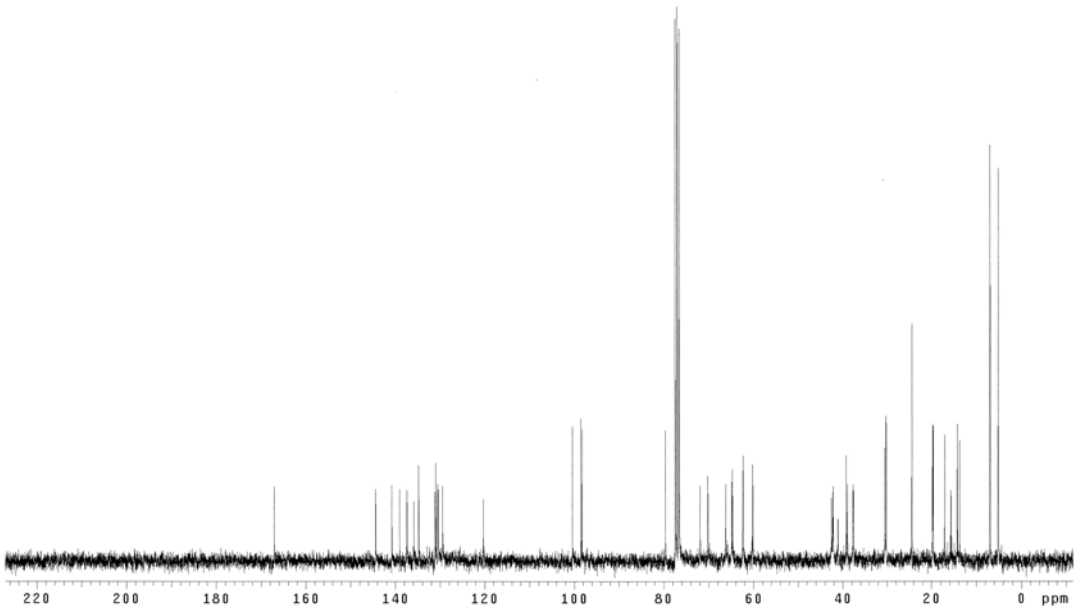
This entire experimental procedure was performed in the dark. To a stirred solution of EtO2C(CH=CH)3CH2PO(OEt)2 (34 mg, 0.111 mmol, 300 mol%) in THF (1.11 mL. 0.1 M) was added LHMDS (0.11 mL, 1.0 M in THF, 0.111 mmol, 300 mol%) at -78 ^{o}C. The reaction mixture was stirred for 30 min at -78 ^{o}C, and a solution of 4.16 (28 mg, 0.037 mmol, 100 mol%) in THF (0.37 mL. 0.1 M) was added slowly -78 ^{o}C. The resulting solution was stirred for 30 min at -78 ^{o}C and gradually warmed to ambient temperature. The reaction mixture was stirred for an additional 8 hr, and then quenched with saturated aq. NH_4Cl. The resulting solution was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:7 to 1:5 with 0.1% TEA) to give 4.17 (59 mg, 0.067 mmol) as a yellow oil in 61% yield.

TLC (SiO_2): R_f = 0.55 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = -11.0 (*c* = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.59 (dd, *J* = 14.4, 11.2 Hz, 1H), 6.42 (dd, *J* = 14.0, 10.4 Hz, 1H), 6.34-6.25 (m, 3H), 6.20 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.85 (d, *J* = 14.8 Hz, 1H), 5.74 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.62 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.49 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.28-4.36 (m, 1H), 4.20 (q, *J* =7.2 Hz, 2H), 4.10-3.96 (m, 4H), 3.96-3.86 (m, 1H), 3.76-3.68 (m, 1H), 3.20-3.12 (m, 1H), 2.37-2.33 (m, 2H), 1.74-1.67 (m, 1H), 1.56-1.44 (m, 8H), 1.43 (s, 3H), 1.38 (s, 6H), 1.33 (s, 3H), 1.31 (s, 6H), 1.28-1.21 (m, 4H), 1.03-0.87 (m, 24H), 0.59 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 144.4, 140.8, 139.0, 137.4, 135.9, 134.8, 131.2, 131.0, 130.6, 130.5, 129.5, 120.3, 100.4, 98.6, 98.3, 79.6, 71.9, 70.2, 66.2, 64.9, 64.7, 62.4, 62.3, 60.2, 42.6, 42.3, 42.1, 41.1, 39.2, 38.9, 37.6, 30.5, 30.2, 30.1, 24.4, 19.8, 19.7,19.6, 17.1, 15.7, 14.3, 13.7, 6.9, 5.1. FTIR (neat): υ 3510, 2952, 2875, 1708, 1622, 1578, 1459, 1379, 1300, 1248, 1224, 1199, 1168, 1128, 1007, 937, 912, 874, 817, 737 cm^{-1}. HRMS (ESI) Calcd. for $C_{51}H_{86}O_{10}Si$ $[M+Na]^+$: 909.5882, Found: 909.5880.

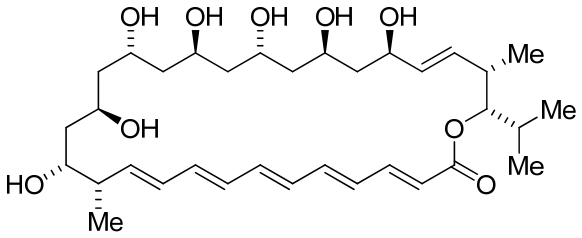
^{1}H NMR



^{13}C NMR



(3*E*,5*E*,7*E*,9*E*,11*E*,13*S*,14*R*,16*R*,18*R*,20*S*,22*S*,24*R*,26*R*,27*E*,29*S*,30*S*)-14,16,18,20,22,24,26-heptahydroxy-30-isopropyl-13,29-dimethyloxacyclotriaconta-3,5,7,9,11,27-hexaen-2-one



(+)-roxaticin

This entire experimental procedure was performed in the dark. To a stirred solution of **4.17** (59 mg, 0.067 mmol, 100 mol%) in 4:1:1 THF/MeOH/H_2O (3.35 mL, 0.02 M) was added LiOH (0.34 mL, 1.0 M in H_2O, 0.335 mmol, 500 mol%) at ambient temperature. The reaction mixture was stirred for 6 hr at ambient temperature, and diluted with saturated aq. NH_4Cl. The resulting solution was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo.

The resulting seco-acid was employed directly in the next reaction. To a stirred solution of the seco-acid in THF (3.35 mL, 0.02 M) were added Et_3N (19 μL, 0.134 mmol, 200 mol%) and 2,4,6-trichlrobenzoyl chloride (16 μL, 0.101 mmol, 150 mol%). The reaction mixture was stirred for 3 hr at ambient temperature, filtered through the pad of celite and diluted with toluene (10 mL). This solution was added over a period of 8 hr using a syringe pump to a solution of 4-dimethylaminopyridine (327 mg, 2.68 mmol, 4000 mol%) in toluene (133 mL, 0.02 M) at 50 ^oC. The reaction mixture was stirred for

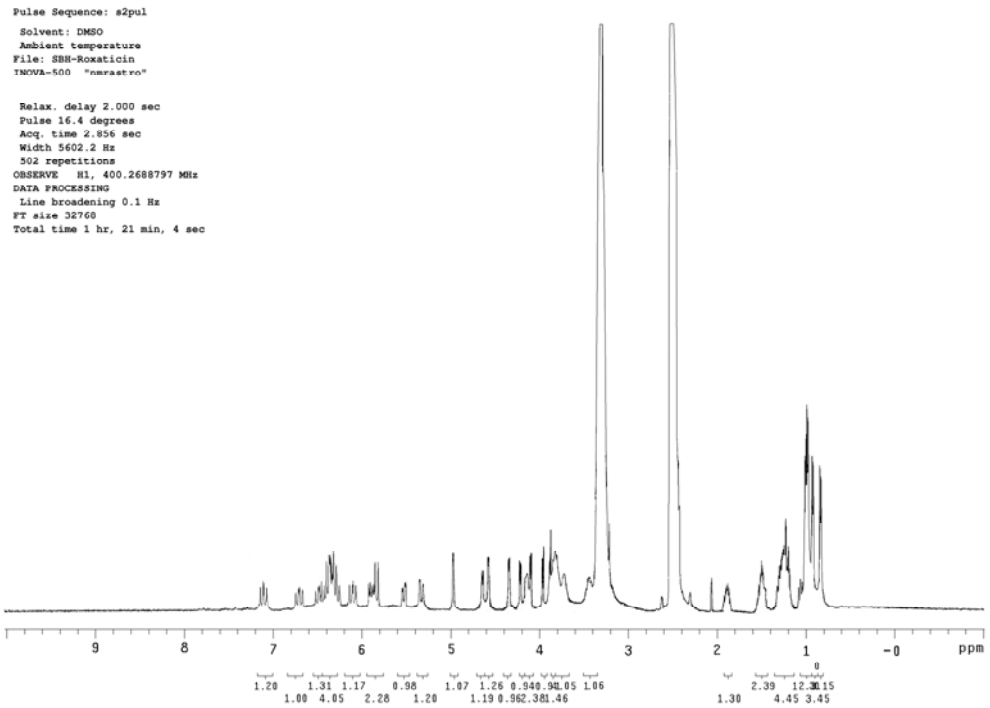
an additional 4 hr, and toluene was removed under reduced pressure. The cloudy oil was diluted in 1:1 hexanes/ethyl acetate, filtered through a silica plug over a pad of celite and washed with 1:1 hexanes/ethyl acetate, then concentrated under reduced pressure to afford a bright yellow oil. The resulting oil was used directly in the next reaction.

A solution of protected crude roxaticin in MeOH (5 mL) was treated with Dowex 50Wx8 acidic resin (100 mg). After being stirred for 4 hr, the mixture was filtered and concentrated in vacuo. Purification by preparative reverse-phase thin-layer chromatography (RP-18, 100x100x0.25 mm, two plate, 10% H_2O/MeOH) gave **(+)-roxaticin** (12.6 mg, 0.0208 mmol, 31% yield) as a yellow solid.

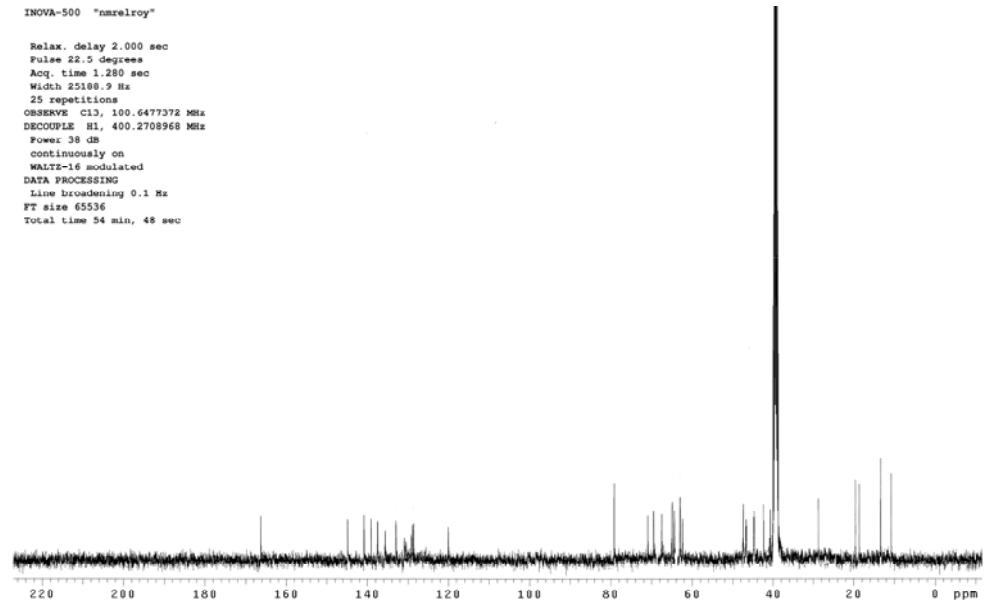
$[\alpha]_D^{26}$ = +11.3 (*c* = 0.17, dioxane).[26] ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.11 (dd, *J* = 15.6, 11.6 Hz, 1H), 6.69 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.47 (dd, *J* = 14.4, 11.2 Hz, 1H), 6.42-6.26 (m, 4H), 6.10 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.88 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.82 (d, *J* = 15.2 Hz, 1H), 5.54 (dd, *J* = 15.6, 5.1 Hz, 1H), 5.34 (dd, *J* = 16.0, 3.6 Hz, 1H), 5.01 (s, 1H), 4.65 (dd, *J* = 7.2, 2.5 Hz, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 1H), 4.20 (d, *J* = 5.4 Hz, 1H), 4.15 (m, 1H), 4.12 (d, *J* = 5.0 Hz, 1H), 3.93 (d, *J* = 5.8 Hz, 1H), 3.84 (m, 1H), 3.98-3.72 (m, 5H), 3.42 (m, 1H), 2.55 (m, 2H), 1.86 (m 1H), 1.48 (m, 2H), 1.40-0.99 (m, 10H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 144.6, 141.1,139.2, 137.6, 135.7, 133.1, 131.0, 130.4, 129.4, 129.1, 128.7, 120.2, 79.3, 71.0, 69.8, 67.7, 64.9, 64.3, 62.9, 62.4, 47.3, 46.7, 46.6, 44.4, 44.3, 42.6, 40.9, 35.7, 28.8, 19.7, 18.7, 13.7, 10.8. FTIR (neat): υ 3410, 1708, 1612, 1588, 1379, 1304, 1268, 1138, 1007,

933, 910, 872, 737 cm^{-1}. HRMS (ESI) Calcd. for $C_{41}H_{73}O_9Si_1$ $[M+Na]^+$: 629.3600, Found: 629.3663.

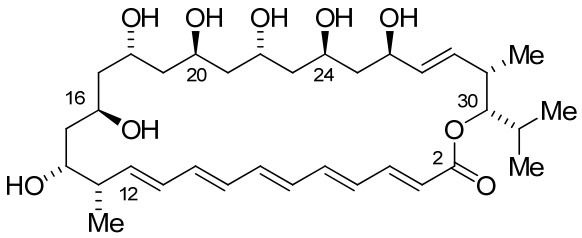
^1H NMR



^{13}C NMR



^{1}H NMR Comparison for Roxaticin (d_6-DMSO)



	Natural Roxaticin	Krische	Rychnovsky	Mori	Evans
Me2CH	0.84 (d, 6.5)	0.84 (d, 6.6)	0.83 (d, 6.1)	0.84 (d, 6.6)	0.84 (d, 6.6)
Me2CH	0.93 (d, 6.5)	0.92 (d, 6.6)	0.92 (d, 7.3)	0.93 (d, 6.6)	0.92 (d, 7.0)
C13-**Me**	0.99 (d, 6.5)	0.98 (d, 6.6)	0.97 (d, 7.3)	0.99 (d, 6.7)	0.97 (d, 6.6)
C29-**Me**	1.01 (d, 7.5)	1.00 (d, 6.9)	1.00 (d, 6.1)	1.01 (d, 6.8)	1.00 (d, 7.0)
H15,17,19,21,23,25	0.95-1.34, 1.16-1.34, 1.49 (m)	0.99-1.40, 1.48 (m)	1.00-1.30 (m), 1.49 (m)	1.00-1.40, 1.49 (m)	0.99-1.32, 1.48 (m)
Me2C***H***	1.87 (m)	1.86 (m)	1.86 (m)	1.87 (m)	1.86 (m)
H13,29	2.55 (m)	2.55 (m)	2.55 (m)	2.55 (m)	2.55 (m)
H14,16,18,20,22,24	3.42, 3.71-3.89 (m)	3.42, 3.72-3.98 (m)	3.42, 3.73 (s)	3.42, 3.71-3.98 (m)	3.42, 3.83 (m)
CH***OH***	3.88 (d, 6.0)	3.84 (m)	3.83 (m)	3.87 (d, 4.6)	3.83 (m)
CH***OH***	3.94 (d, 6.0)	3.93 (d, 5.8)	3.93 (d, 6.1)	3.93 (d, 5.6)	3.93 (d, 5.9)
CH***OH***	4.13 (d, 6.0)	4.12 (d, 5.0)	4.11 (d, 4.9)	4.12 (d, 5.1)	4.11 (d, 4.4)
H26	4.16 (m)	4.15 (m)	4.15 (m)	4.15 (m)	4.15 (m)
CH***OH***	4.22 (d, 5.0)	4.20 (d, 5.4)	4.20 (d, 4.9)	4.21 (d, 5.4)	4.20 (d, 5.9)
CH***OH***	4.38 (d, 4.5)	4.36 (d, 4.0)	4.35 (d, 3.7)	4.36 (d, 3.9)	4.36 (d, 4.4)
CH***OH***	4.60 (d, 4.0)	4.59 (d, 3.6)	4.58 (d, 3.7)	4.59 (d, 2.9)	4.59 (d, 3.7)
H30	4.66 (dd, 7.0, 2.5)	4.65 (dd, 7.2, 2.5)	4.64 (d, 7.3)	4.66 (dd, 9.5, 2.5)	4.64 (dd, 7.0, 2.6)
CH***OH***	5.00 (d, 2.5)	5.01 (s)	4.98 (s)	4.99 (s)	4.99 (s)
H28	5.35 (dd, 15.5, 3.0)	5.34 (dd, 16.0, 3.6)	5.34 (d, 15.9)	5.35 (dd, 16.4, 3.6)	5.33 (dd, 15.8, 3.3)
H27	5.55 (dd, 15.5, 4.4)	5.54 (dd, 15.6, 5.1)	5.50 (dd, 15.9, 3.7)	5.55 (dd, 15.4, 5.1)	5.53 (dd, 15.5, 5.0)
H3	5.83 (d, 15.5)	5.82 (d, 15.2)	5.81 (d, 14.6)	5.83 (d, 15.1)	5.82 (d, 15.0)
H12	5.89 (dd, 15.5, 7.0)	5.88 (dd, 15.6, 7.2)	5.87 (dd, 14.6, 6.1)	5.89 (dd, 15.1, 7.3)	5.89 (dd, 15.1, 7.0)
H11	6.12 (dd, 15.5, 10.0)	6.10 (dd, 15.2, 10.0)	6.10 (dd, 14.6, 11.0)	6.12 (dd, 15.4, 10.7)	6.10 (dd, 14.4, 11.2)
H9	6.28 (dd, 15.5, 10.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H7	6.33 (dd, 14.5, 10.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H10	6.36 (dd, 15.0, 10.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H5	6.40 (dd, 15.0, 11.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H8	6.48 (dd, 14.5, 10.0)	6.47 (dd, 14.4, 11.2)	6.47 (dd, 14.6, 11.0)	6.48 (dd, 15.1, 10.7)	6.47 (dd, 14.4, 11.2)
H6	6.70 (dd, 15.0, 10.0)	6.69 (dd, 15.2, 10.8)	6.69 (dd, 14.6, 11.0)	6.70 (dd, 14.4, 11.2)	6.70 (dd, 14.4, 11.2)
H4	7.13 (dd, 15.5, 11.0)	7.11 (dd, 15.6, 11.6)	7.11 (dd, 15.9, 12.2)	7.12 (dd, 15.4, 11.7)	7.11 (dd, 15.5, 11.7)

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Chapter 1

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